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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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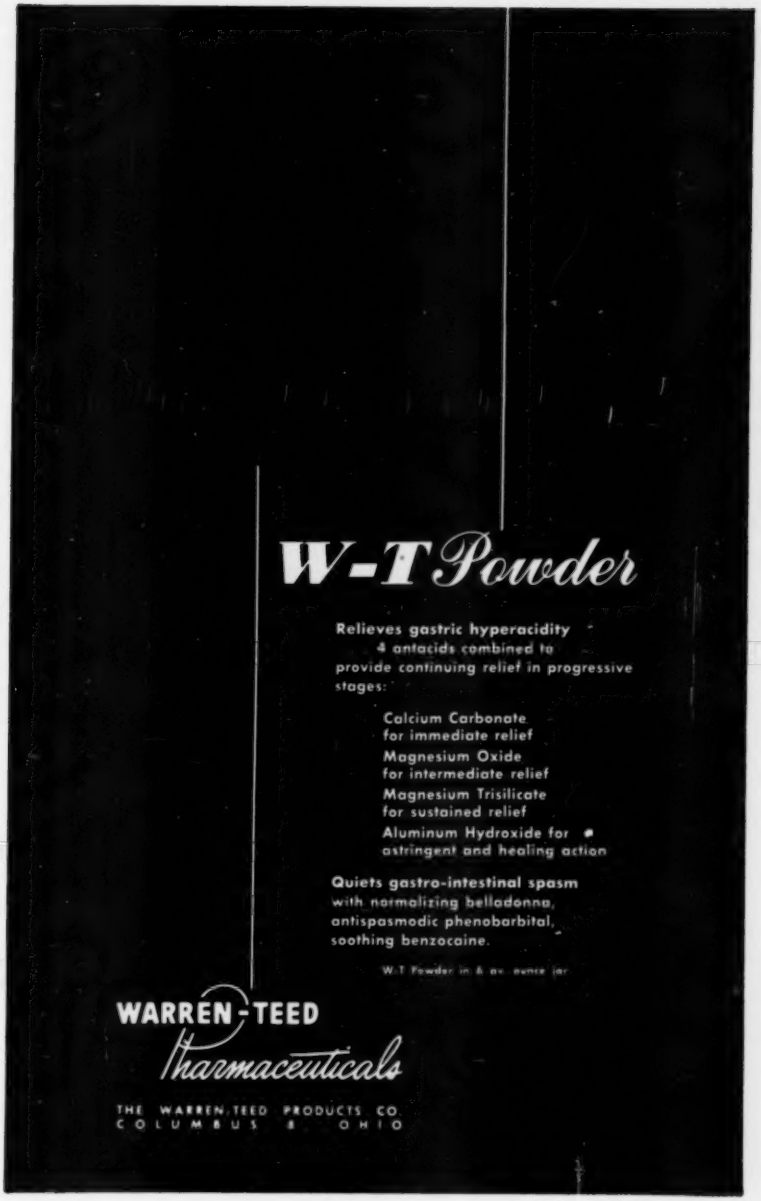
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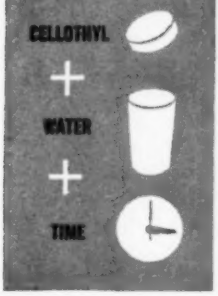

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1. Bargen, J. A.: Gastroenterology **13**:275 (Oct.) 1949.

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BULLETIN OF
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PUBLIC HEALTH ASPECTS IN THE DEVELOPMENT OF ATOMIC ENERGY

*The Hermann M. Biggs Memorial Lecture**

SHIELDS WARREN

Director, Division of Biology and Medicine, U. S. Atomic Energy Commission

TEN YEARS AGO the hazards of ionizing radiation were of concern to a relatively small group of radiologists, their nurses, technicians and their patients; and a small industrial group of dial painters. The total amount of radium available was on the order of two pounds. Today, radioactivity is a matter of concern to hundreds of scientists, thousands of industrial workers and large segments of our population.

Radioactive materials in the atomic energy program are being handled in amounts equivalent to hundreds of tons of radium. Radioactive isotopes of different half lives and different characteristics of the radioactivity emitted from them are being widely used in science and to a limited extent in technology. It is, therefore, of small wonder that there is very real concern in the public health field with regard to this new potentially hazardous material.

There has just been established a new radiological health branch of the United States Public Health Service in recognition of the new prob-

* Delivered before The New York Academy of Medicine, April 6, 1950.

lems that confront us. However, these problems are more potential than actual. For the first time a major industrial development, that of atomic energy, has recognized possible dangers in advance and so controlled them as to make them virtually nonexistent. The Manhattan Engineering District was so wisely advised by Dr. Robert S. Stone, Dr. Stafford L. Warren, Colonel James P. Cooney and others of their medical group that the hazards of handling radiation were recognized in advance and effectively controlled.

Under the Manhattan District, while its operations involved handling the equivalent of hundreds of tons of radioactive materials there were only two deaths from ionizing radiation. The Atomic Energy Commission has had no deaths from this cause. This is indeed a heartening record, to see that a major hazard that only 25 years ago was virtually unrecognized has been effectively controlled. Some of you will recall the cases of cataract that regrettably have developed in some cyclotron workers and are now appearing in some of the survivors at Nagasaki and Hiroshima. In every instance materially more radiation was received than the permissible dose.

It is important that in our desire to continue the excellent record we do not lose perspective. There is great danger because atomic energy is new, because it is spectacular, that we focus on it more attention than it properly deserves. Actually, there are far more hazards in the hospital bacteriological laboratory, both to laboratory personnel and to the community, than in the radiation laboratory using isotopes.

There is one very fortunate thing: our instruments for radioactivity are so delicate that there is an enormous factor of safety between detectable radiation and radiation that will do harm. For example, the average therapeutic dose of radioactive phosphorus is from 3 to 5 mc. Yet, we have instruments that will detect one millionth of this.

There is a great tendency in the mind of the public to confuse the presence of radioactivity in minute degrees with danger. However, we each receive in an average American city in the course of a lifetime somewhere around 2 roentgens from cosmic radiation. We receive 0.2 of a milliroentgen per day internally from the potassium that is a normal constituent of the body.

Experience has taught us that the current permissible dose for external ionizing radiation, 0.3 r per week, is not only safe but gives an appreciable factor of safety.

There are those who are concerned about the genetic effects of minute but continued amounts of radiation. So far as can be determined, in light of present knowledge, if we keep exposure to radiation within the permissible range, genetic harm will not result. On the basis of Evans' calculations, it is highly unlikely that any detectable increase in congenital anomalies will result even after many generations, if a small fraction of the population receives daily radiation doses up to 0.1 r per day, twice the current permissible dose level in atomic energy establishments. On the basis of single doses of radiation in somewhat larger amounts, it is extremely unlikely that significant changes will appear even in case of the less severely exposed of the surviving populations of Hiroshima and Nagasaki. The geneticists are unwilling to assume that any striking increase in abnormalities will appear and the observations of the Atomic Bomb Casualty Commission, a subdivision of the National Research Council supported by the Atomic Energy Commission, show that there is as yet no increase in abnormalities among those populations. The best calculations of the geneticists who have been consulted on this problem is that in all probability in the second and third generation there will be no more than a doubling of the usual incidence of significant abnormalities; in other words, an increase perhaps from one per thousand births to 2 per thousand births.

This state of control of an extensive industrial operation has not been easily achieved. It has meant complicated engineering, the development of remote control apparatus, the enormous increase in costs to provide safety by means of shielding, ventilation and other types of protection. It has, in some instances, even slowed production and added to the difficulty of solving the engineering problems already almost overwhelming in themselves. These costs, these delays have been well worth while in the safety that they have given.

We have still unanswered problems as how best to control the use of radioactive isotopes in other than the atomic energy installations.

We have the problem of the radioactive wastes from the atomic energy installations. These are not problems entirely solved, nor yet are they problems to which there is no safe and immediate answer.

First, let us consider the problem of the handling of isotopes. They are distributed from Oak Ridge only after the Isotope Distribution Committee, an advisory committee of the Atomic Energy Commission, has satisfied itself that the prospective user is familiar with isotopes and

their handling and has adequate facilities for their satisfactory utilization and disposal.

In waste disposal, whether from the Atomic Energy Commission plants or the users of radioactive isotopes in hospitals, universities and other laboratories, there are several facets.

One, how to dispose of liquid wastes; two, how to dispose of solid wastes; three, how to prevent excessive amounts of gaseous radioactive materials from escaping into the atmosphere.

One general principle in dealing with materials of shorter half-life is to store them for a period before disposing of them which results in a marked lowering of activity. For example, in the case of radioactive iodine every eight days of storage reduces its activity by half. In case of isotopes with longer half-lives, this period of storage is of less help in the disposal problem.

In the case of liquid wastes, dilution can be resorted to and small amounts of radioactive substances can be satisfactorily disposed of by way of the sewer without danger. In fact, sanitary engineers use radioactive isotopes to follow the flow and sedimentation of sewage.

There has been some concern expressed as to the possible effect that radioactive materials will have on the biologic processes essential to satisfactory operation of certain types of sewage disposal plants. The experiments carried out thus far indicate that far higher levels of radiation than any that reasonably might be expected to be encountered would be required before interference results.

In the case of solid wastes or apparatus contaminated by long-lived radioactive materials, secluded and properly safe-guarded burial grounds are indicated. In case of gaseous wastes most of the materials commonly encountered are of short half life. Dilutions in air with or without a period of preliminary holding very largely eliminates these.

One of the dangers that needs to be considered in all disposal problems is that certain bacteria, plants or animals have the power of accumulating various chemical elements, so that one has to weigh the potential danger that a diluted radioactive isotope may subsequently be reaccumulated to some degree. The dilution factors recommended take due cognizance of this point.

The general philosophy of the Atomic Energy Commission has been that no agency should create a hazard, monitor that hazard and attempt to control it independently. As fast as the limits placed by national

security permit, the Atomic Energy Commission has declassified information bearing on this problem, has developed and made available instruments for radiation detection, has trained personnel so that there may be qualified persons in the field and has encouraged the implementation and the utilization of the normal control mechanisms.

To be specific, the Atomic Energy Commission has developed a series of high-activity level and low-activity level counters for the detection of the different types of radiation. It has trained physicians, public health officers, medical officers of the armed services, physicists, chemists and other scientific groups in how to detect the presence of radioactivity and how to interpret the amount found.

In coöperating with state health officers it keeps them informed as to the shipments of radioactive isotopes being made within their state. It has worked closely with sanitary engineering and the Commission's own sanitary engineer, Mr. Arthur Gorman, has done fine work in the preparation of standards, in the guidance of research and in the transmission of knowledge to his colleagues.

The Atomic Energy Commission particularly welcomes the establishment by the Public Health Service of its radiological health branch with the hope that this branch may take over some of the functions that up to the present time the Commission itself has been forced to carry.

The story of public health and atomic energy would not be complete if I were not to remind you that there are other hazards in the operations of atomic energy than those of radiation alone. Perhaps the most spectacular of these encountered is the hazard due to exposure to beryllium. When the Atomic Energy Commission first began to use beryllium in quantity, the then available information indicated that it was a harmless substance. Our experience as well as that of the fluorescent lamp industry soon demonstrated that not only would the metal produce acute pneumonitis but chronic lesions in the lung and elsewhere as well, some of these lesions fatal. Berylliosis is now recognized, now largely controlled.

In the light of current experience the standards now set will prevent the acute disease and we believe the chronic as well.

Atomic energy will become more and more a part of our everyday life. We must learn to live with it. A part of that burden rests on your shoulders.

THE BORDERLAND OF EMBRYOLOGY AND PATHOLOGY

*The Middleton-Goldsmith Lecture**

RUPERT ALLAN WILLIS

Formerly Sir William H. Collins Professor of Human and Comparative Pathology, Royal College of Surgeons; Pathologist to the Royal Cancer Hospital, London, England

INTRODUCTION

WHILE on the one hand pathology is, rightly enough, the handmaid of medicine, on the other hand she is also a science in her own right. We pathologists are thus not only technicians and advisers to the clinician; we are, or should be, also biological scientists, interested in the fundamental properties of living matter in both disease and health. It is good for us periodically to leave the hospital ward and laboratory, and to take a birds-eye survey of progress in related branches of biology which, we may be sure, will have important bearings on our own. One of the most relevant of these is *embryology;* and my intention in this lecture is to show the significance for pathology of discoveries made by experimental embryologists since the beginning of the present century.[1]

Epigenesis versus Preformation: Of fundamental significance for both embryology and pathology is the concept of *epigenesis*, namely that the egg is a simple structure which does not contain any kind of preformed representation of adult structure and that embryonic development consists in a progressive creation of complex structure stage by stage. This principle was clearly enunciated by Aristotle in the fifth century B.C., and again 2,000 years later by William Harvey who in his "De generatione animalium" (1651) said of the egg "no part of the future offspring exists *de facto*, but all parts inhere *in potentia*." Again, vertebrates "are made by epigenesis, or the superaddition of parts." . . . "A certain order is observed according to the dignity and use of parts, . . . as a ship is made from a keel, and as a potter makes a vessel."

As we shall see, modern experimental embryology has fully con-

* Delivered before the New York Pathological Society, December 16, 1949.

firmed the principle of epigenetic development. Healthy eggs are *not* predetermined to grow into healthy adults, for various injurious agencies in the environment of the egg and embryo can interfere with its development and lead to malformations or other anomalies. Most of the recent experimental work in this field has been done on amphibian embryos, so that it is necessary to recall briefly the early development of the amphibian egg.

Early Embryonic Development

The Amphibian Egg: Even before fertilization the frog's egg has polarity; one hemisphere is pigmented, the other pale. The pigmented pole will become the future head end of the embryo, and the pale pole laden with yolk will become the hind end. Apart from this polarity, the cytoplasm of the egg is undifferentiated.

Fertilization does three important things; it brings into the fertilized egg the paternal hereditary factors; it activates the egg to begin its development, and it determines the plane of bilateral symmetry. The mid-ventral line of the embryo forms at the meridian where the sperm enters the egg, while on the opposite or dorsal side, a little below the equator, there appears after fertilization a grey crescentic area which is of great importance in subsequent development. After fertilization then, the zygote, though still an undivided cell, has all its main axes and its right and left sides determined.

Segmentation now ensues; successive mitotic divisions convert the fertilized egg into a berry-like cluster of smaller cells or blastomeres, a *blastula*. The cells of the pigmented hemisphere of the blastula are smaller than the yolk-laden blastomeres of the lower hemisphere; yolk appears to retard cell-division.

A highly important step in differentiation now takes place in the region of the grey crescent. The surface cells of the cranial hemisphere proliferate rapidly, spread downwards, and invaginate themselves into the interior in the region of the grey crescent (Fig. 1). This invagination, called *gastrulation*, produces a cavity, the archenteron or primitive gut, which opens to the exterior by an aperture, the blastopore. The cranial or dorsal lip of the blastopore is the region of most active invagination, and is a region of fundamental importance in early development. The diving in or invagination of surface cells at the dorsal lip is an autonomous process, for isolated pieces of the lip, when transplanted

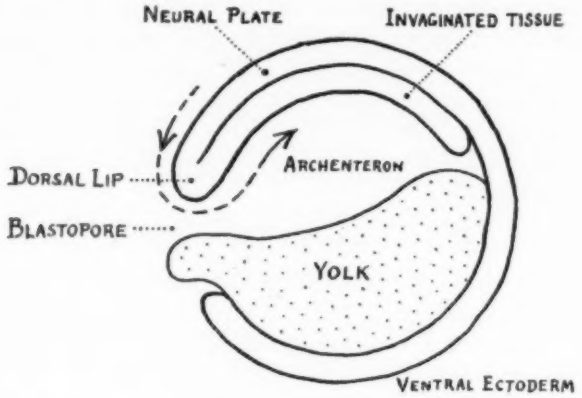

Fig. 1—Diagrammatic mid-line section of frog gastrula, showing invagination of tissue at dorsal lip of blastopore.

to the surface of another embryo, promptly dive inwards in the same way. The cells which invaginate in the mid-line at the dorsal lip give rise to important axial structures of the embryo, the primitive gut roof, the notochord and the paraxial mesoderm or future myotomes. Meanwhile, internally the entoderm and mesoderm are becoming differentiated; so that gastrulation finally results in the delamination of the primary germ layers, the ectoderm externally, endoderm lining the archenteron, and the mesoderm between.

Presumptive Organ Regions in the Blastula: It is possible to map out on the surface of the blastula the regions which normally will become the various organs of the future embryo. By making small injuries or by staining small patches on the surface of the blastula with intra-vitam stains, and then following the subsequent movements and fates of the injured or stained regions, the amphibian blastula has been mapped completely in terms of organ rudiments. We may call these areas *presumptive organs*—presumptive notochord, brain, spinal cord, and so on. The distribution of these presumptive organ areas on the surface of the blastula is quite unlike their adult relationships, which are achieved by the extensive mass movements during gastrulation.

After gastrulation and delamination of germ-layers are complete, the arrangement of organ rudiments is essentially that of the adult. The

plate of neural tissue which now lies along the dorsal side of the gastrula soon presents two parallel longitudinal folds which rise up and fuse dorsally to enclose the neural tube. When this has lost its connection with the surface, the entire surface of the embryo is clothed by epidermis, and the rudiments of all other structures lie internally in roughly their permanent positions. From the time the neural folds appear, the young embryo, which meanwhile is undergoing elongation, is called a *neurula.*

Early Plasticity and Later Non-plasticity or Chemo-differentiation of Tissues: When we speak of the "presumptive" organ rudiments in the blastula, we imply that, given normal development, the regions in question are destined to become particular organs. By transplantation experiments, however, it is found that, up to the middle stage of gastrulation, the prospective fates of most regions are *not* irrevocably fixed. A piece of presumptive neural tube, taken from its embryo and grafted into the side of another, will differentiate into epidermis in accord with its new surroundings, or conversely, a piece of presumptive epidermis grafted into the presumptive neural region of another embryo will differentiate into part of the brain, spinal cord or eye according to its position. Even the germ layers are interchangeable in the blastula or early gastrula. Up to the middle stage of gastrulation, then, the tissues are still plastic or undetermined as regards their final differentiation; each part has potentialities for differentiation much wider than it ever displays in normal development.

During later gastrulation, however, the various regions begin to lose their plasticity. Their prospective differentiation becomes irrevocably determined, and a piece of any given presumptive rudiment, wherever grafted, will now differentiate only into the tissues of that rudiment. A presumptive limb area from a late gastrula or neurula, grafted into an abnormal situation, will continue to form a limb; presumptive epidermis will proceed to form skin wherever it may be transplanted; and a presumptive eye rudiment grafted into the body cavity will produce an eye there. Some change, as yet invisible and presumably chemical in nature, has taken place in each region and has fixed its prospective fate. This change, which precedes visible histological differentiation, is called *chemo-differentiation.* It results in the embryo becoming a patchwork or mosaic of separately determined, though to some extent overlapping, regions; and it is a progressive process, the mosaic coming

to consist of more and smaller pieces as development proceeds.

The Primary Organizer and Axiation: One region of prime importance in the fertilized egg and blastula is exempt from the rule that the different parts of the early embryo are indeterminate or plastic. This is the grey crescent, which gives origin to the dorsal lip of the blastopore, and which from the beginning is destined irrevocably to invaginate beneath the surface and to form the essential axial structures.

The grey crescent or dorsal lip is remarkable, not only because of its inflexible presumptive fate, but also because it has the power of inducing neighboring plastic tissues to disregard their former presumptive fates and to participate in the formation of the main axial and paraxial structures of an organized embryo. Thus, as the classical experiments of Spemann and Mangold (1924)[2] showed, if a small fragment of dorsal lip is grafted into the front or side of another embryo in the blastula or early gastrula stage, it at once invaginates itself and induces the neighboring host tissues to take part in forming a secondary embryo in the body wall of the host embryo. The grafted dorsal lip tissue itself always forms the notochord and usually some of the paraxial mesoderm of the secondary embryo; but the plastic host tissues around, under the inductive influence of the grafted dorsal lip, may produce neural tube, eyes, ears, mesodermal somites, and pronephric tubules. Because of its remarkable power of inducing the formation of the main axial and paraxial parts of an embryo, the dorsal lip tissue was given the name of "*primary organizer.*"

As might be suspected, the organizer is of fundamental importance in normal development, to which indeed it is essential. An egg or blastula deprived of its grey crescent region, or a group of blastomeres isolated from a blastula before they have been affected by the primary organizer, grows and differentiates into a variety of tissues but these form only an unorganized medley. The differentiations attained by such unorganized masses of cells must depend on "labile determinations" of the cells themselves. The organizer is then a directive centre, dictating the fate of neighboring tissues, and integrating all the main changes in early development, particularly those involved in gastrulation and axiation.

One of the most immediate effects of the primary organizer is to induce the formation of the neural plate and tube in the overlying ectoderm. All of the gastrular ectoderm underlain by invaginated

organizer—notochord and paraxial mesoderm—will become neural. Further, the organizer's inductive effects on the overlying ectoderm show distinct regional differences. The first tissue to be invaginated at the dorsal lip of the blastopore reaches furthest forward into the head region, and this tissue induces the formation of cephalic structures—brain, eyes, ears—from the overlying ectoderm. Later invaginated "trunk organizer" will induce only spinal cord and not brain or eyes.

The Nature of the Primary Organizer: The action of the amphibian organizer is *not* species-specific; it can induce the formation of a secondary embryo even when grafted into an embryo of a species different from its own. Organizer material killed by heat, drying or alcohol still has inductive power; so also has a piece of agar or gelatine which has lain in contact with inductive tissue. Cell-free extracts of organizer material are potent, and the solubilities of the active ingredients suggest that they are sterols. Clearly then the activity of the organizer is due to chemical substances which it elaborates. Future research must isolate and identify these substances, and investigate the conditions under which they are active or inactive.

The Organizer in Birds and Mammals: In birds and mammals the homologue of the amphibian blastopore is the *primitive streak* along with the *primitive node and pit*. These structures give rise to the notochord and paraxial mesoderm; and experiments prove that the avian primitive streak has inductive powers similar to those of the amphibian organizer. Like the latter also, it is not species-specific, and it retains its activity after coagulation by heat.

Embryologists have long known that Hensen's node or primitive knot at the anterior end of the avian or mammalian primitive streak is an important centre of growth. From it the notochordal or head process invaginates and grows forward beneath the ectoderm. The primitive pit, which appears just behind the node and which becomes the neurenteric canal, is the homologue of the blastopore, and Hensen's node is its dorsal lip. The lateral lips and their prolongation posteriorly, the primitive streak, are the main growth centres of the embryonic mesoderm.

Secondary Induction; Dependent Differentiation: The dorsal lip of the amphibian blastopore or the avian primitive streak is the *primary organizer*, because it initiates the whole complex process of somatic organization and because its inductive capacity is a primary one not de-

pendent on any earlier organizer. But, after primary organization has been determined during gastrulation, many tissues other than the derivatives of the primary organizer play the part of *secondary organizers* in that they exert inductive influences, presumably chemical in nature, on neighboring plastic tissues, which therefore undergo *dependent differentiation.* The classical example (Spemann, 1901[3]) is the dependence of lens formation on the presence of the optic cup. The lens of the vertebrate eye develops as a localized thickening of the embryonic ectoderm overlying the optic cup, the outgrowth from the brain which gives origin to the retina and optic nerve. If the optic cup is removed before the lens has formed, no lens appears; and an optic cup transplanted under the skin elsewhere induces the formation of a lens from the overlying epidermis.

There is no doubt that similar inductive influences operate in many developing organs. The post-gastrular embryo is a complex mosaic of interacting parts. The fates of most of these are already determined in broad outline, but there are still subordinate tissues the complete differentiation of which is dependent on the proper development of other tissues. These latter are *secondary organizers,*[4a] and their inductive effects on neighboring parts depend, like the inductive effect of the primary organizer, on chemical substances elaborated by them. "There is, then, a whole hierarchy of organizers or morphogenetic hormones functioning in development." (Needham[4b]).

Experimental Extirpation of Parts of Embryos: If an amphibian embryo after gastrulation is transected each part will continue its prospective development, the front part forming a head only and the hind part a trunk and tail only. If in the early tail-bud stage the bud is cut off, a healthy organism will develop but with a permanently deficient tail. Removal of rudiments of eyes, limbs, spinal cord, pituitary or other parts results in permanent lack of these structures later. By appropriate operations on the early embryo almost any desired defect can be produced in the developed organism.

Experimental Transplantation of Organ-Rudiments: Almost all organ-rudiments and tissues of amphibian, avian or mammalian embryos are capable of self-differentiation when suitably transplanted or when suitably cultivated *in vitro.* In the chick, grafting of embryonic rudiments on the chorio-allantoic membrane of another egg has shown that isolated ears, eyes, part or whole limb-rudiments, parts of brain and

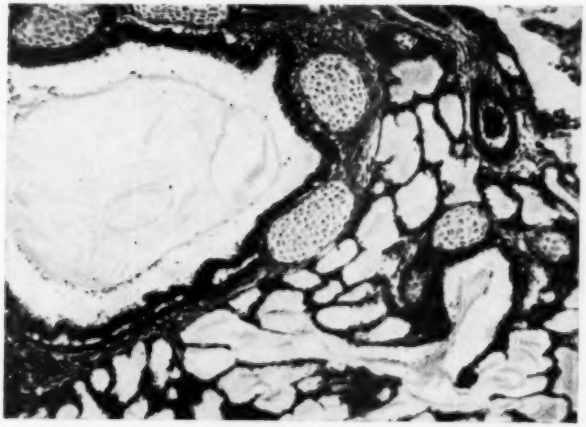

Fig. 2—Well differentiated lung tissue with bronchi and alveoli, 2 weeks after intracerebral transplantation of lung rudiment of a 6 mm. rat embryo.

spinal cord, lung, etc., grow and differentiate well. In amphibia the mosaic determination of various regions has been demonstrated mainly by grafting them in abnormal positions in other embryos, in which as they develop they attain their proper prospective fates independent of their new environment.

Some experiments of my own[5] proved very successful in demonstrating the powers of self-differentiation of isolated tissues and organ-rudiments from mammalian embryos. Finely minced tissues or selected whole organ-rudiments from rat embryos were implanted through a wide-bore needle into the brain or cranial cavity of young adult rats. The host rats were killed after intervals of from 1 to 3 months and the grafts studied. It was found that almost all kinds of embryo tissues grew and differentiated as well in their foreign sites as they would have done in normal development. Good growth and differentiation of the following structures were obtained: skin, sebaceous and sweat glands, hairs, tongue-epithelium, conjunctiva, whole teeth, cartilage, pieces of bone, bone marrow, whole bones, bronchi and lung, stomach, pancreas, intestine, prostate, lachrymal gland, mucous glands, salivary glands, thyroid, pituitary gland, testis and epididymis, thymus, striated muscle,

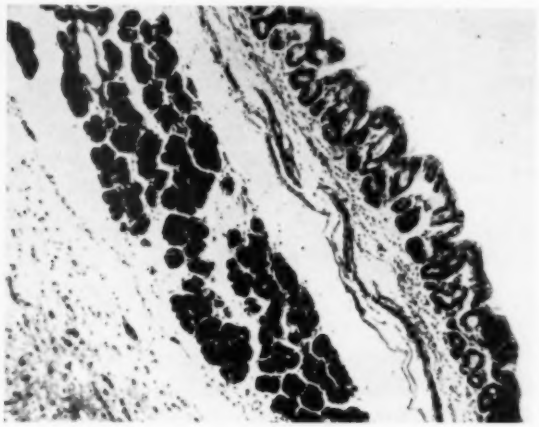

Fig. 3—Well differentiated stomach and pancreas 2 weeks after intracerebral transplantation of rudiments of these organs of a 6 mm. rat embryo.

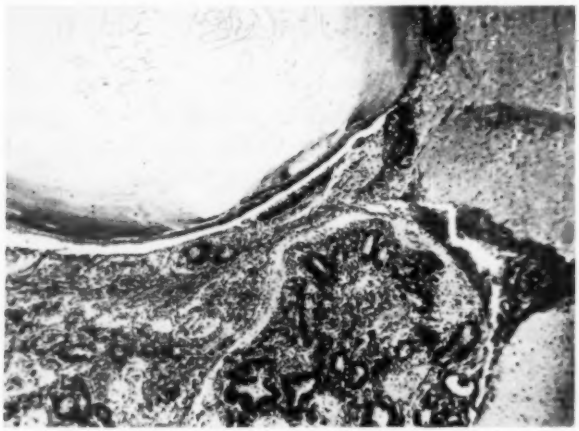

Fig. 4—Lens and retinal tissue 4 weeks after intracerebral transplantation of eye rudiment of a 10 mm. rat embryo.

lens, retina and cochlea (Figs. 2-4). In all experiments the differentiated tissues which developed in the grafts corresponded strictly to the region of the embryo which had been transplanted.

It may be mentioned here that the experimental implantation of embryo tissues into adults has long been practiced by experimental pathologists in the hope of verifying Cohnheim's hypothesis that tumors arose from embryonic "cell-rests," or in the hope of shedding light on the genesis of teratomas. Both of these hopes are false: grafted embryo cells do not give rise to tumors; and the mixtures of tissues in differentiating embryo grafts are not comparable with spontaneous teratomas, the genesis of which must be sought rather in disordered chemistry in the early embryo.

Cultivation of Organ-Rudiments in vitro: Many kinds of organ-rudiments have been grown successfully in culture media. Amphibian notochord, neural tube, muscle, skin, gut, liver, pancreas, etc., have shown normal differentiation during their periods of survival in culture. Pieces of gut differentiated in culture have shown peristaltic movements, and pieces of heart have begun to pulsate. Whole heart-rudiments have developed sinus, auricle, ventricle and aortic bulb. Organ-rudiments from chick embryos and from mammalian embryos also have shown successful growth and differentiation *in vitro*. For example, the early cartilaginous rudiments of the chick's femur will grow into a recognizable femur increasing its bulk 30-fold or more and showing normal ossification.

Teratology, the Pathology of the Embryo

Teratology Distinguished from Foetal Pathology: In 1904 Ballantyne[6] stressed the distinction between the pathology of the foetus and the pathology of the embryo. Broadly speaking the foetus, with its differentiated parts and tissues, resembles an adult in miniature, and the reactions of its tissues to injuries, poisons and infections are similar to those of the adult. But the embryo is structurally and functionally unlike an adult. "The great, almost the only, function of the embryo is to form tissues and organs, or, in one word, organogenesis." Hence, the pathology of the embryo is unlike that of the foetus; it is *teratology*. Just as the chief activity of the embryo is the formation of parts and organs, so the effects of pathogenic agents in the embryo are malformations of parts and organs.

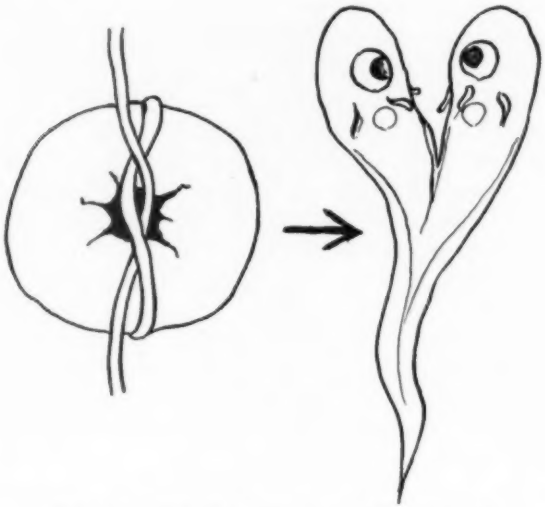

Fig. 5—Diagram of Spemann's experimental production of anterior duplication of newt embryo by ligature of blastula vertically through the blastopore.

This conception of the distinction between embryonic and foetal pathology has been confirmed by experimental embryologists. Many kinds of malformations can be produced experimentally by exposing embryos of suitable ages to abnormal environments. The abnormal conditions capable of causing malformations are very diverse, and include many agents which produce "diseases" in the developed organism, e.g., trauma, oxygen deficiency, abnormal temperatures, various chemical substances, and pathogenic organisms. Let us look at some of the experimental results, commencing with the grossest malformations of all, double monsters.

The Experimental Production of Double Monsters and other Major Malformations: Double monsters have been produced in many different ways, the chief of which are as follows:

(a) *By interference with the zygote during early segmentation,* e.g., in Amphioxus by shaking and disarranging the blastomeres, and in the frog by inverting the egg at the 2-cell stage.

(b) *By partial constriction of the embryo during gastrulation.* Spemann showed that if the early newt embryo is constricted in the median plane during gastrulation, the resulting embryo will show anterior duplication, i.e., it will have two well-formed heads joining with a single hind end at varying levels. The explanation is clear: the invaginating organizer, moving anteriorly from the dorsal lip of the blastopore, meets an obstacle in the constriction and therefore bifurcates, one-half of it going forward on either side of the constriction. The Y-shaped invaginated organizer induces a Y-shaped embryo, with duplicated head regions (Fig. 5). If the plane of constriction of the blastula is not accurately median, but slightly oblique, then one head of the resulting double monster is normal and the other is incomplete and usually cyclopic. The greater the obliquity of the constriction, the greater the imperfection of the malformed head.

(c) *By oxygen deficiency or lowered temperature.* By these means, Stockard[7] caused retardation of development during early cleavage of trout and minnow embryos, and produced a great variety of major malformations, including double monsters, cyclopia, malformed brains, eyes and viscera. These results were traceable to irregular and delayed segmentation of blastomeres occasioned by the developmental arrest.

(d) *By delayed fertilization.* Witschi[8] found that if fertilization of frog's eggs was delayed, various abnormalities resulted. Brief delay resulted in an abnormal sex ratio in the resulting tadpoles, males predominating. Longer delay of fertilization resulted in the production of double monsters and sometimes of teratoma-like growths. The double monsters were traceable to abnormalities of cleavage and to splitting of the blastopore lip at the onset of gastrulation.

All the foregoing methods of producing double monsters involve treatment of the embryos at very early—pregastrulation—stages. "When eggs are treated at later stages, as at the beginning of gastrulation, no double monsters will occur, their moment has passed." (Stockard[7]). Duplication of the axis of the body, of any degree, presupposes corresponding duplication of the inducer of axiation, the primary organizer. Double monsters are malformations of primary axiation and can only be produced therefore by disturbances affecting the embryo prior to establishment of its axis. Once the axis is laid down, the embryo has become a mosaic of organ-fields, the future differentiation of each of which is determined; and no amount of interference can produce more

axis tissue.

Experimental Malformations in the Mosaic Embryo: As already noted, after the stage of mosaic determination of a particular organ-field, extirpation or damage within that field will lead to permanent defects or deformities of the organ. Similar defects can be obtained by oxygen deficiency, lowered temperature or chemical poisons applied to the embryo at appropriate stages during or after gastrulation. By these means, the experimentalist can produce, in amphibian or fish embryos, the main axiation of which has developed normally, cyclopia, deformed mouths, nostrils, gills, brains or viscera. The particular malformations produced depend, not on the kind of abnormal agent used, but on the time at which it is applied.

Thus, experimental work has verified Ballantyne's[6] prescient opinion that malformations "are the results of morbid agents . . . acting upon such parts of the organism as are in the embryonic or formative stage." Stockard[7] expressed the same principle when he spoke of "developmental arrests at *critical* stages, . . . when certain important developmental steps are in rapid progress or are just ready to enter upon rapid changes."

Developmental arrest: Many malformations are developmental arrests in the sense that they consist in non-formation of parts, persistence of parts which should have disappeared, non-union of parts which should have coalesced, or failures of canalization.

A special group of developmental arrests, probably related to deficiency of the circulation in the embryo and early foetus, has been studied by Streeter[9] and by Sir Arthur Keith,[10] namely the deficiencies of the limbs to which the name "intra-uterine amputation" used to be applied in the mistaken belief that they were due to constriction by "amniotic bands." "In these cases sharply circumscribed areas of limb-bud tissue are of such inferior quality that only imperfect histogenesis occurs. Whether injured in some way or defective from the outset, and the latter is probably true, these areas maintain themselves only in the earlier weeks of pregnancy. Already at the fourteenth week they are found as fibrous moribund masses, surviving after the manner of tissue-cultures and sloughing away from the adjoining normal tissues. . . . The defects if present in one extremity tend to be in all four, which would be expected on the basis of a general deficiency in the limb-bud tissue. The defects tend to be in the distal portions of the extremities."

Sir Arthur Keith[10] extended the conception of Streeter's "foetal

dysplasia" to many other kinds of malformations—facial clefts and scars of obscure origin, anencephaly, spina bifida and meningocele; and advanced the view that "all such lesions are caused by a local necrosis probably due to a circulatory failure which may be placental in origin. The failure occurs along marginal areas where capillary formation is in progress. . . . 'Amniotic adhesions' are never formed by a failure in the separation of the amnion from the embryo, but are always produced by and from the foetus—as a result of dysplasia in foetal tissues. They are the result, not the cause, of foetal malformations." Perhaps impaired circulation may underlie also such failures of coalescence as cleft palate, coloboma, hypospadias, and other local arrests of growth movements.

Specificity of Some Factors Causing Malformations: While it is certainly true that identical malformations may result from widely different agents, yet there is also evidence that some of these agents selectively damage certain embryonic tissues.

A good example of this is afforded by the recent discovery that German measles affecting a woman during the first two or three months of pregnancy is apt to cause certain characteristic defects in the child, the chief of which are congenital cataracts, cardiac malformations, deaf-mutism, and microcephaly (Swan[11]). Here then we have an example of an infective disease, the virus or toxins of which have a selective damaging effect on certain parts of the embryo or early foetus; the results are, not the disease rubella as it occurs in the adult or child, but certain localized malformations or dystrophies.

Ballantyne[6] collected much evidence that various kinds of maternal infections or toxic diseases, including syphilis, tuberculosis, lead and other chemical poisonings, could damage the embryo or foetus. He recognized that the commonest result of such maternal diseases was foetal death; but he believed that, should the foetus survive, the effects of the damage inflicted on it during early growth might appear as malformations or dystrophies, admitting that it was difficult to prove the culpability of any particular causative agent. The association of malformation with rubella, just cited, is a clear instance in support of Ballantyne's general thesis, and it should stimulate new and more extensive studies, both clinical and experimental, of the possible influence of all kinds of maternal diseases in producing teratological effects.

Foetal and Post-natal Malformations: While it is true that most major malformations take origin in the embryonic period, we must remember

that the distinction between the embryonic and foetal periods is arbitrary. Many parts and tissues are still immature or "embryonic" in the foetal period, and indeed the differentiation of some parts is not complete until long after birth. Thus, adult structure is not attained in the genital system until after puberty, in the skeleton until the epiphyses unite, and in the jaws until the permanent teeth erupt. The immaturity of such parts in childhood is, as it were, a projection of embryonic and foetal development into post-natal life; and in such parts minor malformations theoretically may, and in fact do, sometimes arise from disturbances of late foetal or post-natal development. For example, destruction of an epiphysis will result in arrest of growth in length of the bone, and the stunted bone is as much a malformation as if it had resulted from damage inflicted on the primordium of the bone in the embryo. So also dentigerous cysts and odontomes are malformations brought about by disturbances of dental development during late foetal or post-natal life. The pseudo-hermaphrodite condition of the genitalia resulting from adrenal cortical tumors in the foetus is another example of a malformation acquired relatively late in intra-uterine life.

Metaplasia

We have seen that, while most of the parts of an early pre-gastrular embryo are completely plastic and are capable of differentiating into almost any tissue according to the environment in which they are placed, after gastrulation they lose this nearly total potency and become determined to differentiate into specific structures of the adult body. But, even in the adult, many of the tissues are not immutable, but are capable of limited degrees of divergent differentiation in abnormal proliferative states—in regeneration and in tumors. These transformations, called *metaplasias*, show that a residue of the plasticity of the early embryo persists throughout life.

We need not spend time on detailed examples of metaplasia, which are familiar to all pathologists. Suffice it to recall that in both inflammatory lesions and tumors glandular or mucosal epithelia of various kinds may become squamous; that bone or cartilage may develop in many soft-tissue lesions, such as scars, sclerotic arteries, foci of chronic inflammation or degeneration, and the stroma of some tumors; that in many rarefactive states of bone, bony tissue often suffers transformation into fibrous tissue; and that bone formed by metaplasia in soft tissues

may contain all of the components of haemopoietic bone marrow, which must also be locally produced. Even smooth and striated muscle fibres are not immutable, for, as Carey's experiments[12] showed, by excessive exercise of the dog's bladder its muscle fibres can become striated.

Many adult tissues, then, possess a potential versatility for aberrant differentiation which they do not display under normal conditions, but which are to be looked upon as adaptations to an abnormal environment. These metaplastic adaptations occur only in proliferating cells; they are, as Nicholson[13] maintained, a form of regeneration with atypical differentiation. The proliferating cells "undergo a true rejuvenescence, and . . . some of the earlier potencies are reacquired." Regeneration is indeed resumed embryonic growth, and metaplasias are the visible evidence of resumed embryonic plasticity.

Embryonic Tumors

Truly embryonic tumors are those which arise in early life from tissues that are still undifferentiated and which continue to proliferate at this embryonic level. They include nephroblastoma (Wilms' tumor or embryonic renal tumor), neuroblastoma, retinoblastoma (retinal neuro-epithelioma), hepatoblastoma (embryonic tumor of liver), and the embryonic sarcomas (often rhabdomyosarcomas) of the urogenital organs of children.

The structure of these tumors can be understood only in the light of that of the corresponding tissues at various stages of embryonic development. Thus, nephroblastomas consist of embryonic and foetal renal tissue, in some cases wholly undifferentiated, in others differentiating into tubules, glomeruli and non-epithelial mesenchymal tissues, these last sometimes showing heterotopic differentiation, e.g., into striated muscle. The characteristic fibrillar rosettes of neuroblastomas are similar to those seen in the developing sympathetic ganglia of the embryo and early foetus. Retinoblastomas reproduce the structures of developing retina; their rosettes consist of small cavities corresponding to those of the embryonic optic vesicle into which rod and cone processes project through a characteristic limiting membrane.

Some of these embryonic tumors are called "mixed" because they show differentiation of tissues which do not occur normally in the organs involved, e.g., striated muscle or cartilage in renal or hepatic tumors. But these heterotopic tissues are only such as can readily be

derived from immature mesenchyme (*vide* Metaplasia above). They are never utterly foreign to the part; e.g., nephroblastomas do *not* contain skin, teeth, central nervous tissue, respiratory or alimentary structures, all of which are common in teratomas. The embryonic tumors thus differ from teratomas in having regionally restricted potencies for differentiation—potencies of no greater range than those of the particular tissue of origin.

The causation of embryonic tumors is, as H. G. Wells[14] pointed out, an interesting subject for speculation. Most of the ordinary tumors of adults arise only after prolonged exposure of the tissues to carcinogenic agents; the embryonic tumors arise during actual organogenesis, and clearly their causes must be sought in disturbances of embryonic chemistry—the chemistry of the organizers or growth-hormones which we discussed earlier. When discovered, however, the chemistry of these disturbances may well shed light on the central problem of neoplasia, namely the very nature of the irreversible change in the tumor cell. For this reason alone, the embryonic tumors and the kindred teratomas are of peculiar interest and merit the closest study.

Teratomas

Like the regionally specific embryonic tumors, teratomas also arise during early stages of development from immature tissues, and many of them (the malignant ones) continue to proliferate at the embryonic level and to produce tissues of all degrees of immaturity. But, unlike the regionally specific embryonic tumors, teratomas contain a variety of tissues quite foreign to the part. In malignant teratomas recognition of these tissues necessitates a good knowledge of the normal histology of embryos at all stages of development. Pathologists unfamiliar with normal embryonic histology have often misidentified various teratomatous tissues, e.g., both embryonic choroid plexus and neuro-epithelial tissue have often been called "adenocarcinoma," and the all-embracing name "embryonal carcinoma" has been used as a convenient label for a variety of undifferentiated epithelial tissues in teratomas.

Many speculative hypotheses as to the nature of teratomas have been advanced; and still the most prevalent view is that they are distorted foetuses included within the host or derived from his or her own germ cells. The falsity of this view is shown by the following facts:

1. By topographical reconstructions of whole teratomas, using the

serial slab method employed by the writer,[15] it is found that teratomas, unlike the most degraded of amorphous foetuses, show no signs of the possession of a vertebrate axis, or of delamination of germ-layers, or of regional distribution of organs.

2. Teratomas, again unlike amorphous foetuses, are *neoplasms* with powers of progressive independent growth, extension and metastasis. The advocates of the "foetus" hypothesis ignore this fundamental attribute.

3. Highly organized parts which may occur in a teratoma, e.g., teeth, a loop of intestine, a piece of cerebellum, or digits (Fig. 6),[16] do *not* presuppose a foetus. A spark-plug is a highly organized structure, but its construction does not presuppose the previous construction of a motor car. Complex parts in teratomas result from the local mutual influences of proliferating plastic tissues on one another—influences comparable to those of the secondary organizers in embryogenesis, whereby one growing tissue chemically induces a neighboring plastic tissue to participate in the formation of an organized composite structure. Careful topographical studies of teratomas enable the histogenesis and mutual relationships of the differentiating tissues to be traced.

In nearly all malignant teratomas containing a variety of embryonic tissues, there are frequently present small or extensive areas of a rather characteristic, though quite undifferentiated, component consisting of an irregular closely aggregated meshwork of plump cuboidal cells, with intervening strands of mesenchyme and blood vessels (Fig. 7). This tissue, which has often been vaguely designated "carcinoma" (especially "embryonal carcinoma") is the most primitive embryonic component recognizable in these growths, and its relationships show that it differentiates into a variety of specific tissues—epidermal, dental, neural, probably respiratory and alimentary, and possibly also mesenchymal. If this view is correct, the undifferentiated tissue in question represents the essential primordial element in teratomas; for, like the tissues of the pre-gastrular embryo, it is totipotent embryonic tissue from which all else that is found in these growths may spring. In malignant teratomas containing it, its proliferation continues at this very early embryonic level, simultaneously with partial maturation of parts of it into specific tissues of various kinds. In benign teratomas, containing only fully differentiated tissues, the whole of the primordial tissue has matured and differentiated with the lapse of time. Benignancy or malignancy in

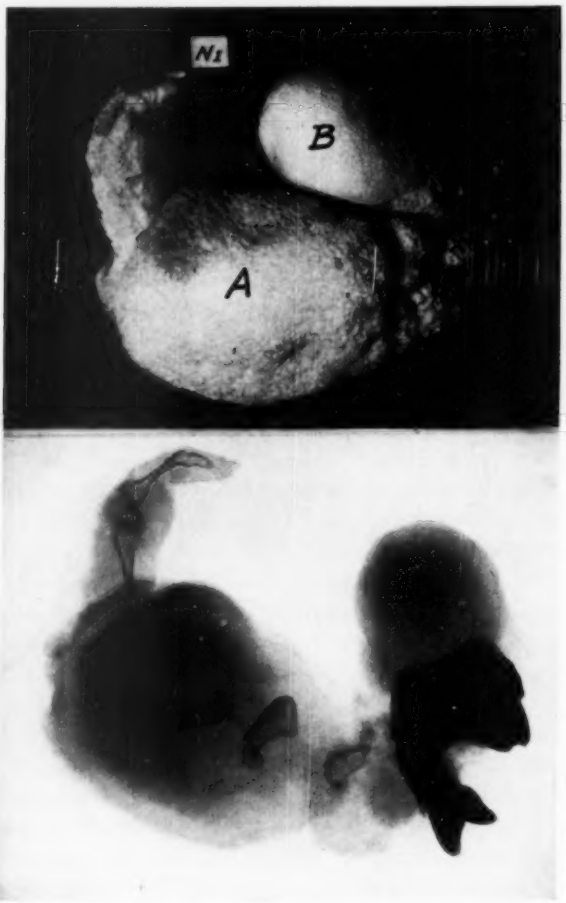

Fig. 6—A digit in a retroperitoneal teratoma. AB is bilobar skin-covered eminence which projected into cyst cavity from pedicle X; N1, a well-formed nail at end of digit. The X-ray photograph shows the phalanges and metacarpal, and also several non-descript bones in the main mass. (Specimen has been described fully by Gale & Willis[2]).

Figure 6 is reproduced with the kind permission of the Editor of the Journal of Pathology and Bacteriology.

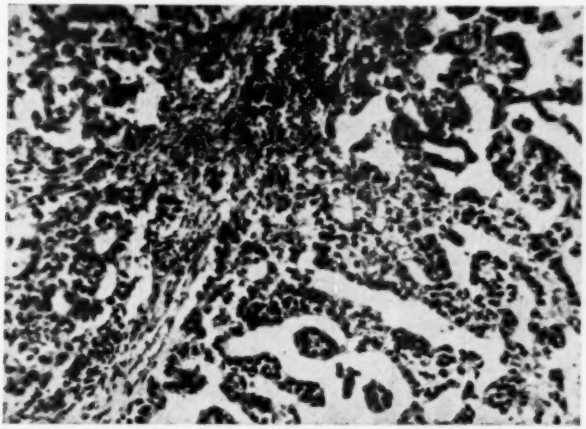

Fig. 7—Undifferentiated embryonic epithelium-like tissue, a frequent component of malignant teratomas.

teratomas is thus related to the success or failure of maturation of their component tissues; and we will understand this only when we learn more of the chemistry of the hierarchy of organizers concerned in embryogenesis. Then, too, we will realize how crude have been our earlier speculations as to the nature and mode of origin of teratomas.

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*PEDIATRIC ASPECTS OF INHALATIONAL THERAPY**

OXYGEN THERAPY IN ACUTE RHEUMATIC CARDITIS IN CHILDREN

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THE physiologic basis for the therapeutic use of oxygen in heart disease lies in the fact that the oxygen tension of the arterial blood may be critically diminished in patients suffering from cardiac disease. The ill effects resulting from myocardial hypoxia are due primarily to the low pressure of free oxygen in the blood to which the cells of the heart muscle are exposed, producing a disturbance in cell metabolism. Inhalation of an oxygen-enriched atmosphere raises the oxygen saturation of the arterial blood to normal in such patients, restoring the oxygen tension and reversing the ill effects of hypoxia. These physiologic principles of oxygen therapy have been summarized by Haldane,[1] Lundsgaard and Van Slyke,[2] Barcroft,[3] Meakins and Davies,[4] Peters and Van Slyke[5] and others.

In 1939, Poulton[6] demonstrated that patients suffering from rheumatic myocarditis showed marked clinical improvement when treated in a 50 per cent oxygen atmosphere. The temperature and pulse rate were lowered; cardiac murmurs were altered; the size of the heart diminished, and significant electrocardiographic changes occurred. He found that the incidence of valvular heart disease was far lower in rheumatic patients who were continuously treated with oxygen during the acute phase of carditis than in the control group of patients. And he pointed out that the physiologic basis for the beneficial results in such cases might be a restitution of the local oxygen want in the diseased heart muscle.

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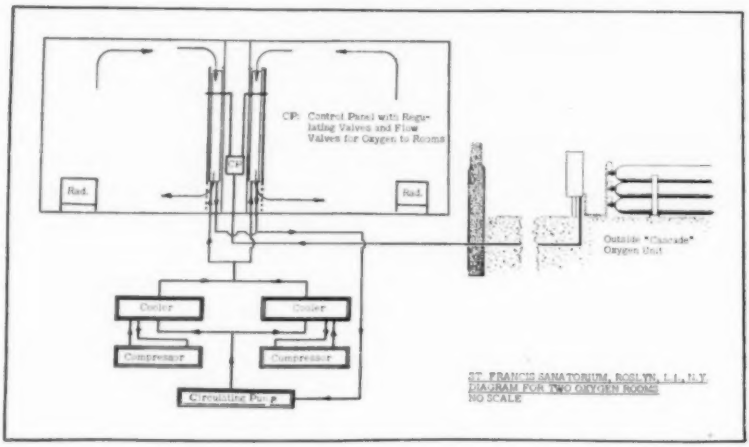

Fig. 1

Six years' experience with oxygen therapy for rheumatic carditis in children at the St. Francis Sanatorium for Cardiac Children confirms in the main the observations of Poulton. In addition, our experience points the way to a more satisfactory method of oxygen administration and to more clearly defined criteria for choosing the patient who might be expected to respond favorably to this form of therapy. It further suggests a physiologic process which may play an important role in the improvement observed in the functional cardiac disability in patients with acute carditis who are treated with oxygen.

At the very start of this experience it became clear that since rheumatic carditis is a protracted illness of months' duration, continuous oxygen therapy would have to be administered for many weeks or months. In long-continued oxygen therapy, our primary consideration in choosing the method of administration was the comfort of the patient. The mask, catheter and tent were poorly tolerated by children and were difficult to control as regards oxygen and carbon dioxide concentration, temperature and humidity. Special oxygen chambers were constructed for this purpose, and these have been used continuously for the past six years (Fig. 1—Table I).

TABLE I—ATMOSPHERIC CONDITIONS IN CHAMBERS

Oxygen Concentration	Av. 50% Fluctuation 47-52%
Carbon Dioxide Concentration	Av. 1.5% Fluctuation 1.3-1.6%
Temperature	Av. 66° F. Fluctuation 64°-68°
Humidity	Av. 75% Fluctuation 70-80%
Barometric Pressure	Normal

TABLE II—OXYGEN THERAPY IN ACUTE RHEUMATIC CARDITIS WITHOUT CONGESTIVE FAILURE (58 CASES)

CLINICAL MANIFESTATIONS OF IMPROVEMENT

Clinical behaviour of patient

- Marked and rapid increase in appetite
- Rapid increase in body weight
- Euphoria and feeling of well-being

Clinical course of acute carditis

- Rapid and significant drop in temperature
- Marked decrease in respiratory rate
- Dramatic and consistent drop in pulse rate
- Stabilization of cardiac rate

Cardiac manifestations

- Stabilization of heart sounds and murmurs
- Subsidence of cardiac symptoms: angina, fatigability, palpitation, and dyspnea on exertion
- Increase in vital capacity
- No evidence of progressive cardiac damage

Electrocardiographic changes

- Disappearance of signs of conduction disturbance
- Consistent disappearance of signs of anoxemia
- Changes in duration of electrical events in cardiac cycle

Results

Over a period of six years, 121 rheumatic children received nearly 11,000 days of oxygen therapy or an average of 90 days per patient. Fifty-eight children of this group responded well to oxygen therapy and showed marked clinical improvement. The remaining 63 patients did not show any palpable improvement or presented signs of marked intolerance to this form of treatment.

Early in this experience, it was observed that patients who have acute rheumatic carditis without congestive failure show significant and often dramatic improvement as a result of this therapy (Table II). All children in this group showed a rapid and marked increase in appetite. Their facial coloring improved, and this was not related to the level of the hemoglobin. They gained weight more rapidly than children in a control group of cases. These children showed an obvious and significant change in their behavior pattern almost as soon as they were introduced into the oxygen chambers. Irritability, nervousness, impatience and capriciousness changed to obvious contentment and cheerfulness. They all showed an apparent sense of well-being irrespective of the degree of rheumatic activity.

A definite and often an immediate drop in temperature and always a significant narrowing of the daily temperature fluctuation were noted. There was a marked slowing of the respiratory rate. After the first twenty-four to forty-eight hours, it was obvious that respiration became less of a task for these patients.

The drop in pulse rate in most patients was immediate and significant. This drop remained constant during the entire period of residence in the oxygen chambers. An intercurrent infection raised the pulse rate only slightly. The labile character of the cardiac rate commonly observed in rheumatic carditis changed to a stable rate, and this stability persisted after oxygen therapy was discontinued. In all patients gallop rhythm and the tumultuous character of the heart action gradually subsided in a much shorter period than would be expected in the natural history of carditis and in a significantly shorter time than was found in a control group of patients treated at complete bed rest at the same institution during the same period of observation.

The frequent alterations in quality of heart sounds and in the character and mode of transmission of murmurs during the course of acute

carditis are well known. In several of these children, mitral diastolic murmurs which were heard for long periods prior to oxygen therapy completely disappeared and were not heard for the entire period of observation. In four instances, aortic diastolic murmurs disappeared toward the end of the period of residence in the oxygen chamber. These changes were observed more frequently and more definitely in the treated group than in the control group of cases.

All patients who presented typical seizures of angina showed significant relief from these attacks during residence in the oxygen rooms. The acute anginal attacks ceased almost at once. In some instances, precordial pain of a milder degree persisted for variable periods, although the associated tachycardia and sense of anxiety completely subsided. In only one instance was anginal pain complained of for several weeks following termination of oxygen therapy.

Cardiac fatigue and dyspnea on exertion in most children subsided after the first few days in the oxygen chambers. Physical activity in bed increased markedly without any effect on respiration or pulse rate. The vital capacity increased significantly, although in some cases it continued to be below normal during the entire course of carditis.

No evidence of progressive heart disease was observed in this group of children. The heart in some cases became measurably smaller; in none larger. There were no signs of progressive endocarditis or functional cardiac disability.

Conduction disturbances subsided rapidly under the influence of oxygen therapy. These changes occurred more rapidly and more definitely than in the control group of patients. Those who showed significant deviations of the ST and T segments prior to oxygen therapy changed to normal configurations within hours or, at most, two to three days after the onset of oxygen therapy. These changes remained unaltered when oxygen therapy was terminated.

Comment

The mechanisms by which these salutary clinical effects are attained in rheumatic carditis are unknown and are now under investigation. A limited number of observations have been made which suggest that improvement in the clinical course of carditis during oxygen therapy is attained by diminishing the burden imposed upon the heart action during the acute inflammatory process of carditis.

TABLE III—GAIN IN DURATION OF DIASTOLE IN RHEUMATIC CARDITIS TREATED WITH OXYGEN THERAPY

Cardiac Rate	*Subject*	*Average Duration of Systole*	*Average Duration of Diastole*	*Gain in Duration of Diastole with Rate Reduction*		
				Per Minute	*Per Hour*	*Per Day*
106 (Av. 24 hr.)	Normal Child	0.305 sec.	0.260			
	Carditis	0.341 sec.	0.221			
86 (Av. 24 hr.)	Normal Child	0.338 sec.	0.360	3.4 sec.	3′ 24″	1h 21′
	Carditis	0.358 sec.	0.339	5.7 sec.	5′ 43″	2h 17′
DIFFERENCE				2.3 sec.	2′ 19″	56′

GAIN IN DURATION OF DIASTOLE PER MINUTE WITH REDUCTION IN CARDIAC RATE FROM 106 TO 86

It is generally agreed that cardiac damage resulting from acute carditis is due to a failure to attain effective cardiac rest during the course of the disease. It is further admitted that prolonged bed rest, sedation, cardiac supportive medication, limitation of physical activity and carefully regimented sanatorium and convalescent care—all these fail in many instances to prevent cardiac damage. Some observers feel that even under the best physical and emotional environment of rest and relaxation, the heart muscle is overactive in acute carditis. This overactivity may be responsible for disturbance in the chemical and mechanical efficiency of the heart muscle. While the accelerated cardiac action may be a compensatory expression of myocardial hypoxia, the accelerated cardiac rate per se may further deplete cardiac efficiency by diminishing diastolic coronary filling and thus increasing the already existing critical anoxemia of the heart muscle.

In a previous communication, we[7] presented evidence to show that overactivity of the cardiac action in acute carditis is expressed in a disturbance of the normal time relationships of systole to diastole. The duration of systole is increased relative to the duration of diastole. We have presented the view that an abnormal prolongation of the period of cardiac contraction without a commensurate increase in the period of relaxation would seem to be an unprofitable physiologic economy for the heart muscle, since the marked decrease in the diastolic period might interfere with oxygenation of the cardiac muscle.

Our experience with oxygen therapy would seem to show that cardiac overactivity in acute carditis is diminished by restoring a more normal relationship in the duration of systole to that of diastole. This is accomplished by a significant prolongation of the diastolic period (Table III). It is reasonable to assume that an increase in the period of cardiac relaxation might tend to bring about a more normal chemical economy of the heart muscle by restoring the normal oxygen balance.

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INHALATIONAL THERAPY IN ACUTE RESPIRATORY INFECTIONS, MEASLES, WHOOPING COUGH AND PNEUMONIA

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THE chief indication for oxygen therapy in infants and children is the existence of relative anoxia or hypoxia. Hypoxia means a lack of sufficient oxygen in the blood and tissues of the body. Its presence is recognized in many ways, chief of which are dyspnea and cyanosis. Hypoxia may be suspected clinically by the presence of tachycardia, flushing of the face, restlessness and abdominal distention.

There are special circumstances in infancy and childhood which may hasten the development of hypoxia in the respiratory diseases proper and in the respiratory complications of certain of the infectious illnesses of childhood such as measles and pertussis. These conditions are: 1) the narrow caliber of the larynx and bronchial tree, which become more easily obstructed the smaller the airway; 2) the inability to expectorate; and 3) the character of the broncho-pulmonary pathology in respiratory diseases and in the respiratory complications of certain infectious processes. This refers to the tendency to bronchiolitis and to diffuse broncho-pneumonia with mucous membrane and interstitial changes, with the resultant tendency to obstructive dyspnea.

The mechanism, or pathological physiology, of hypoxia is first, that an inflammatory reaction in the larynx, bronchi, bronchioles and alveoli produces secretions and narrows the caliber of the bronchi. These interfere with ventilation, that is, the inflow and outflow of air; and the exchange of gases in the alveoli is hindered by the exudate within them. Dyspnea results, and in efforts to overcome it a vicious cycle is set in motion. An attempt is made by the body to increase the depth of respiration; this results in an increased negative intrapulmonary pressure, which in turn increases exudation into the bronchi and alveoli with a further aggravated bronchial obstruction. This causes increased hypoxia and dyspnea. A complicating factor is the tendency to develop

patchy atelectasis because of those special conditions existing in infancy.

An application of these mechanisms of hypoxia will suggest the indications for and the value of oxygen therapy in the management of the respiratory infections and complications in infancy and childhood. There are other advantages to be gained, apart from the ones described, and these will be mentioned as each of the specific infectious diseases is discussed. It must be remembered that not only will oxygen therapy relieve the symptoms of hypoxia but it will also prevent progression of certain pathological processes. It may be stated categorically that in general the advantages of oxygen suggest that it should be used early.

There are three types of apparatus which are best to use for supplying oxygen to infants and children: 1) the large tent; 2) the small hood; and 3) the open oxygen box. The cheapest and easiest of these is the open box. Although this is the simplest apparatus, it is not possible to measure the concentration of oxygen accurately and the humidity is difficult to control. A moderate flow of oxygen results in a therapeutic concentration of the gas at the floor of the box. As Barach[1] has stated, this system may be used particularly for infants because they do not give off as much heat, moisture and carbon dioxide as do adults, and so the usual measures for removal of these constituents are not necessary.

The second method is the small hood. This, in my opinion, is the method of choice for infants. It makes their nursing care much simpler than in a large tent, since, for example, diapering and intravenous therapy can be accomplished without removing the child from an oxygen atmosphere. The third method, the large tent, is preferred for older children. They are happier in a large tent as it obviously offers less restraint. In addition, it permits a greater circulation of air. Other means such as nasal catheters and masks are frightening to young children and will not be tolerated by them.

Whatever method of oxygen administration is used, however, it will be noted that higher temperatures and humidities are prescribed for infants and growing children than for adults, because of their lower production of heat, moisture and carbon dioxide. A concentration of at least 50 per cent and preferably 60 per cent is most desirable and the temperature should be as close to 70° F. as possible. Colder temperatures were formerly advocated, but because they dislike cold air, children cry more and coughing is aggravated. The usual humidity of from 50 to 60 per cent is often insufficient. Under certain circumstances, as in infants

with severe bronchial involvement, a high humidity is desirable and a second oxygen humidifying system should be brought into the tent. A glass cylinder containing tap water is connected by a tube into which flows approximately two to four liters of oxygen per minute. A small nebulizer which contains 3 to 5 cc. of water serves as a source for the fine spray which is forced into the tent through a small glass tube. Saline solution should not be used, as the salt has a tendency to crystallize and therefore may obstruct the tube.

The physical problem involved in the introduction of steam into an increased concentration of oxygen has been solved in a few children's hospitals today with the construction of small steam and oxygen rooms. However, these rooms are impractical because nurses find it uncomfortable to remain in the steamy room.

The use of aerosol solutions presents a further advance in oxygen therapy. The principle of introducing a concentrated medicated vapor directly at the source of the pathologic condition in the bronchi and lungs has been helpful in a few conditions in infancy and childhood. Aerosol may be used either with the aid of a hand nebulizer in which the spray is directed into or in front of the child's mouth; or by means of one which directs the nebulized solutions into the mouth with the aid of a pressure of two to four liters of oxygen per minute. A small flat glass outlet is helpful, as the child will often place it in his own mouth.

Oxygen therapy having been described in general, individual infectious diseases can now be discussed in a specific way.

Acute Respiratory Infections and Pneumonia

In acute laryngo-tracheitis and bronchitis, which most commonly today are on a non-diphtheritic basis, the chief therapeutic agents are first, sulfonamides and antibiotics; second, steam; and third oxygen. In these conditions, commonly called croup, one must see that the child maintains an adequate airway. The alternating use of oxygen and steam is often desirable if the two cannot be used simultaneously.

The question of when to hospitalize such an infant, the choice of antibiotic or sulfonamide, and the indications for tracheotomy are not within the scope of this paper. Suffice it to say that tachycardia, marked restlessness, flushing and increasing cyanosis, in addition to retractions of the suprasternal and xiphoid areas, are indications of trouble and make the use of oxygen imperative.

If a tracheotomy has been done, the endotracheal administration of oxygen may be required and a stream of humidified oxygen is directed so that it passes into the opening of the tracheotomy tube. This will help prevent drying and crusting of the secretions in the trachea.

In infants with capillary bronchitis or bronchiolitis, obstructive dsypnea develops early. When dyspnea, cyanosis and infrasternal and suprasternal retractions occur, there are indications that the airway is being obstructed and extra oxygen must be supplied. If an infant with pneumonia does not respond to specific therapy while in oxygen, it may be that a pleural effusion or pulmonary abscesses have formed. The need for close observation and careful clinical examination is especially important as complications may arise suddenly.

Little has been said in this short review of pulmonary infections in young children about the use of penicillin aerosol. In cystic fibrosis of the pancreas described by Farber[2] and by Andersen[3a] its advantages are unquestionable. Involvement of the lungs is frequent in this condition and can be the cause of death even in those infants whose gastro-intestinal symptoms have been checked. di Sant'Agnese and Anderson[3b] showed that because of the specific pulmonary pathology in fibrocystic disease, penicillin in aerosol solution in doses of 20,000 to 30,000 units four times daily is effective as a prophylactic against secondary infections which are so devastating to the lungs in that condition. An adequate concentration of penicillin can be supplied to the alveoli for months and can be readily maintained by this simple nebulizing procdure, which is painless and takes no longer than ten minutes for each treatment.

Measles

Chemotherapy has controlled most of the secondary infections following measules. Inhalational therapy is needed today only if the patient has a respiratory complication such as edema of the larynx, severe tracheo-bronchitis or pneumonia, or when convulsions occur. The causes of breathing difficulty and the symptoms are the same as those previously mentioned in the description of the acute respiratory diseases.

Whooping Cough

Pertussis presents a difficult problem because the clinical course and physical findings are often deceptive.[4] Involvement of the nose and throat, trachea, bronchi, and lungs in pertussis may be due either to a

combination of organisms or to the Haemophilus pertussis itself. The secondary infecting organism can be adequately treated, as in measles, by penicillin. Oxygen is needed most frequently in the youngest patients —in fact, almost every infant under six months of age will benefit by its use, even though he be afebrile. Even in the summer months, when pyogenic organisms are not prevalent and pertussis is uncomplicated, oxygen in the very young is most essential.

Infants do not react with fever to infections of the respiratory tract to the same degree as do older children and adults. It is surprising how frequently one sees an infant with a temperature of 100° who, when placed in oxygen, will either because of thermal change or decrease of infection drop to a 99° level throughout the day, even without other therapy. A lowered respiratory rate and greater comfort are almost always accomplished under such circumstances. Also, patients with pertussis, and to a lesser extent with measles, cough less when they are in an increased oxygen atmosphere.

Since the respiratory rate in infants is particularly rapid in whooping cough, repeated examination of the chest is indicated when there is interference with normal ventilation. Roentgenograms are a great help, for infants may have extensive atelectasis or pneumonia with clinical signs not much different from those present in a mild tracheitis. The presence of any pulmonary infiltration with dyspnea, even without cyanosis, indicates beginning hypoxia and calls for oxygen.

Excellent nursing is required while the infant with pertussis is in an oxygen tent or hood, for, although the paroxysms may be less frequent, one cannot hear them as well, since the young infant with whooping cough does not cough loudly. In fact, paroxysms can sometimes be seen without being heard at all. There may be frequent long and exhausting paroxysms, following which there is a long period of apnea and cyanosis. Oxygen is especially needed following one of these episodes.

The paroxysmal stage of pertussis may last from two to four weeks, and it is not unusual for infants to be kept in an increased oxygen atmosphere during much of that time. During convalescence, the oxygen content can be lowered, or the child removed from the tent or hood for short periods of time. However, following an extensive paroxysm or vomiting, or after being fed, when there is likely to be distention and consequently some interference with pulmonary ventilation, replacement of the infant into an oxygen atmosphere is desirable.

Sudden withdrawal of a child who has been in an atmosphere of 60 per cent oxygen is not infrequently followed by cyanosis, discomfort and excessive coughing. For that reason it is advisable at feeding time, and at other times when a child must be removed, to turn the oxygen off gradually so as to allow the content in the tent or hood to fall slowly. The child should be replaced in the tent or hood as quickly as possible.

The duration of oxygen therapy in pertussis is determined by the general condition of the child, by the degree of dyspnea and cyanosis, or by the presence of extensive pneumonia and atelectasis. The period of oxygen therapy in pertussis may vary from a few minutes following each paroxysm, to the continued use of the tent for six weeks.

There is need for oxygen if cerebral involvement occurs. Dolgopol[5] has called attention to the role of hypoxia in the etiology of this condition.

Summary

Whatever the etiology, oxygen is needed when there is a state of anoxia or hypoxia. The direct evidence of hypoxia is dyspnea and cyanosis. Hypoxia may be present even without visible cyanosis. There are special conditions in infancy and childhood which may hasten the onset of hypoxia in the course of respiratory illnesses and complications. It is better to supply oxygen early than to delay its use until cyanosis, restlessness and tachycardia have become extreme.

Oxygen may be administered to infants and children by various methods, and in some instances warm moist air and aerosols may be part of the therapy. In diseases such as pneumonia and measles, the need for oxygen for the disease itself does not arise as often as in former times because of the use of sulfonamides and antibiotics, but in pertussis and in acute laryngo-tracheitis, oxygen is a prime therapeutic agent.

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OXYGEN AS A SUPPORTIVE THERAPY IN FETAL ANOXIA

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THE most secure insurance against fetal anoxia is adequate, spontaneous respiration [of the newborn] immediately after birth. The absence of normal ventilation and crying has led to urgent and painstaking efforts to substitute artificial respiration with oxygen by a large variety of methods. It cannot be overemphasized that intermittent pulmonary inflation with oxygen at safe pressures is the most effective therapeutic means available in overcoming fetal anoxia. It is the purpose of the present communication, however, to examine the role of oxygen in the physiological recovery of the fetus and the therapy of fetal anoxia from the dual aspect of some recent newer knowledge and a critical appraisal of the results of current research.

In spite of a steady improvement in neonatal mortality during the past twenty years, there has been almost no decrease in the deaths during the first twenty-four hours after birth.[1] Is this because we do not understand the fundamental causes of death during this period or because we do not apply what is already known? For a variety of reasons, oxygen lack plays the major role in over half the deaths, and the basic treatment for oxygen want is well known. The widespread application of such treatment is sadly lacking. The junior house officer, who is usually left to handle the resuscitative problem, has received instruction only from his immediate superior in the principles of resuscitation, or not at all. It should be the joint responsibility of departments of obstetrics, pediatrics and anesthesiology to offer instruction to the internes and residents in all three departments, irrespective of which one takes the initiative for such teaching. Too often emphasis is placed on a certain type of equipment or on certain stimulating drugs while the basic principles of prompt action, the maintenance of a free airway and getting oxygen into the newborn baby are overlooked. Our own specialty has been negligent in exhibiting an interest in this fascinating field and too often obstetrical anesthesia is left to a most inexperienced group.

The anoxia problem has been outlined and discussed most clearly and unemotionally by Smith[2] in Volume III of Advances in Pediatrics. The only practical method of recognizing fetal anoxia before delivery is through the occurrence of a bradycardia. Other commonly-used diagnostic signs, such as tachycardia and increase in fetal movements, have not been substantiated experimentally.[3] Some method of recording the fetal heart rate continuously in human subjects would be a material aid in recognizing fetal anoxia, but so far neither electrocardiographic nor electronic auscultatory methods have been successful. Waters and Harris,[4] Lund[5] and Barcroft[6] have all demonstrated clearly that the administration of oxygen to the mother between contractions will correct to a large degree the bradycardia of the fetus during labor pains. This simple treatment is not present-day practice in large, busy obstetrical clinics, but should be instituted especially in situations in which neonatal mortality is especially high, i.e., prematurity, multiple births and toxemias of pregnancy.

At the time of delivery, an infant who is apneic, breathes feebly or with occasional deep gasps needs oxygen. The presence of cyanosis, pallor, flaccidity and bradycardia merely corroborates this need. The use of gravity and gentle pharyngeal suction should precede the administration of oxygen. Actual pulmonary inflation can be obtained in countless ways, from the ever-available mouth-to-mouth insufflation to the latest type of mechanical device. Endotracheal suction and inflation are rarely necessary but should be performed quickly and atraumatically by someone well accustomed to the technique. Obviously, the training program mentioned previously should include practical experience with the technique of these procedures.

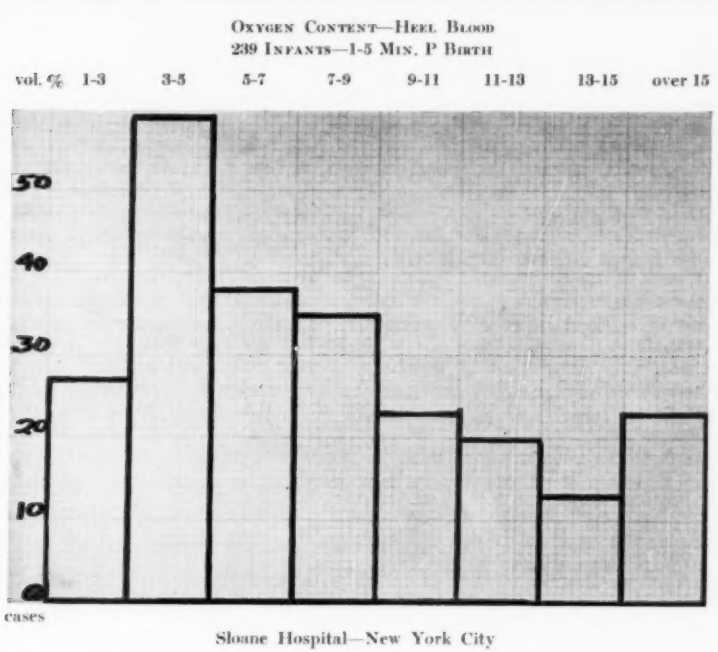
The damage caused by a period of anoxia at birth has been the subject of many papers. True results are elusive because of the nature of the complications. Psychological maldevelopment is indeed hard to evaluate unless the series is large and the controls are ample. The infants who are adequately oxygenated at birth should be followed as assiduously as those who are anoxic. Environmental and hereditary considerations further complicate interpretation. Objective neurological signs are more accurately interpreted but again a large series of cases is needed. Prolonged studies such as those begun in several cities, notably Washington and New York, will be enlightening and may produce other unexpected signs of damage. It is surprising that no metabolic complica-

tions have been noted as a result of fetal anoxia. Negative evidence will be as valuable as positive, and reports of the development of a brilliant intellect in spite of anoxia at birth, as in a case cited by Barcroft,[6] will need elucidation.

The remarkable resistance of the fetus to anoxia has been demonstrated in many ways in several species, and the explanation of this fact is nearing completion. In the rabbit, dog and guinea pig the survival time of fetuses of mothers breathing 100 per cent nitrogen was related to the stage of development rather than to the species.[7] Removal of the medulla is less quickly fatal to newborn small laboratory animals than to the adult.[8] The pattern of oxygen consumption in various parts of the newborn animal's brain is the opposite of that of the adult, the cortical metabolic rate reversing itself from a low to a high figure.[9] It is probable that some mechanism for anaerobic oxidation exists, for the survival time of fetal animals is not improved under anoxic conditions if the anaerobic use of sugar is withheld. The existence of such a mechanism would help to explain why even more damage does not occur after fetal anoxia, but in no way does its presence excuse negligence in administering oxygen to a newborn infant when the need is clinically indicated. No data at all are available to explain the greater tolerance of the *human* fetus to prenatal anoxia.

The numerous difficulties of embarking upon a study in human beings are obvious. The obstetrical and anesthetic problems are inversely proportionate to the skill of the operator. Detailed records of the prenatal problems and an accurately kept chart of the events occurring during delivery call for additional personnel. Simultaneous studies of the maternal and fetal blood are desirable. The meticulous technique needed for the study of samples of intact cord blood, well described by Barcroft,[6] are not applicable to the usual delivery. A deep heel puncture in the infant supplies a blood sample so closely similar to arterial blood samples that this method has proven practicable. The Roughton-Scholander[10] analysis of the blood sample drawn under oil is relatively reliable. Possibly correction for the type of anesthetic gas in use should be made.

The accompanying chart reveals the distribution of oxygen content in volumes per cent, as determined from an initial sampling of blood by the method just described, made within five minutes of delivery of the head in 239 consecutive, unselected vaginal deliveries. If ten volumes per cent is the true average figure for the human newborn infant, the causes



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for our lower mean value 8.0 per cent must be uncovered and corrected. Follow-up studies on these infants in the Pediatric Clinic is planned for a period of five years.

Summary

The problem of fetal anoxia has been only partially solved in clinical practice. The explanations for the persistence of a relatively higher anoxic mortality in the first day of life are twofold. First, there is the failure to employ adequate methods of artificial ventilation with oxygen promptly after birth. Second, there is still a great deal to learn about the physiology of respiration during and after the birth process. Some information based upon the oxygen content of newborn blood has been added in this presentation. The importance of the low values observed is not entirely clear at the present time. It is possible that they suggest the presence of effective anaerobic metabolism.

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THE USE OF OXYGEN IN COMATOSE STATES*

HURLEY LEE MOTLEY

THE essential factors related to the maintenance of normal tissue oxygen tension and to the adequate removal of carbon dioxide have been evaluated from measurements obtained on arterial blood and expired air. The adequate removal of carbon dioxide constitutes an important aspect of the respiratory gas exchange. The arterial oxygen saturation may be maintained near normal by the administration of oxygen, yet the carbon dioxide removal may be hampered by inadequate ventilation or interference with the transfer of gases in the lungs. The two main factors to be considered in oxygen therapy are: 1) an inspired oxygen partial pressure (pO_2) of sufficient magnitude to saturate the arterial blood (normal 96 to 98 per cent[1]) and 2) an adequate ventilation providing sufficiently uniform alveolar aeration to wash out the carbon dioxide. This latter is determined from measurement of total ventilation in liters per minute, the partial pressure of carbon dioxide in the arterial blood (pCO_2) and arterial blood pH. If the arterial blood hemoglobin is from 96 to 98 per cent saturated and the carbon dioxide partial pressure and pH are within the normal range, the respiratory gas exchange is adequate.

The direct determination of the tension of oxygen (pO_2) and carbon dioxide (pCO_2) in arterial blood[2] has been most helpful in studying the transport of oxygen to the blood. The difference between the mean oxygen partial pressure of inspired air (150 mm.Hg average at sea level) and that of the alveolus is referred to as the *aeration gradient*, and the difference between mean oxygen partial pressure of the alveolus and that of the arterial blood is designated as the *transfer gradient*.[3] The term *transfer gradient* has been used because this value deals with the movement of oxygen from the gaseous state in the alveolus either to combination with hemoglobin or to solution in the blood plasma.

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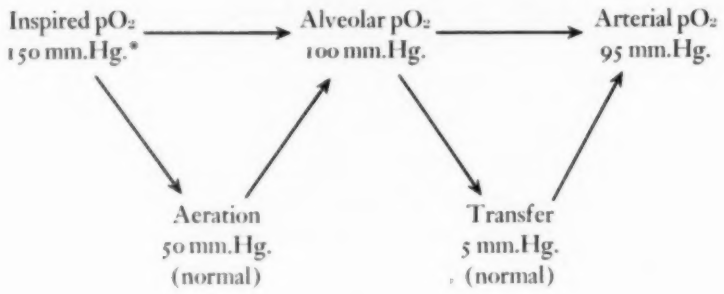
OXYGEN TRANSPORT IN THE LUNGS



Elevation of the transfer gradient designates changes in the alveolar-arterial oxygen gradient from all causes, including the true diffusion difficulty with an increased resistance of the pulmonary membrane.

Factors interfering with the oxygen respiratory gas exchange are primarily those related to mixing, dilution, diffusion and distribution. Decreased ventilation (reduction in vital capacity, maximal breathing capacity or both), increased residual air (pulmonary emphysema with the mixing and dilution problem), impaired diffusion due to increased resistance in the pulmonary membrane (as seen in acute pulmonary edema) and distribution (unequal alveolar aeration and perfusion) are the factors most often responsible for lowering the arterial oxygen tension and saturation.

Increased residual air, decreased ventilation, retained secretions and bronchospasm increase the aeration gradient and lower the alveolar pO_2 and arterial oxygen saturation. Hyperventilation will lower the aeration gradient and raise the alveolar pO_2. Any factor increasing the resistance to the movement of oxygen across the pulmonary membrane (as pulmonary edema) lowers the arterial pO_2 and increases the transfer gradient. Gross venous admixture such as occurs in congenital cardiac anomalies and arteriovenous fistulae produces very high transfer gradients (often over 50 mm.Hg) and arterial blood unsaturation even when the subject breathes 100 per cent oxygen. Unequal alveolar aeration and perfusion (the distribution factor) are a common cause of elevation of the transfer gradient. Fibrosis produces various degrees of

* Ambient air breathing at sea level, barometric pressure 760 mm.Hg.

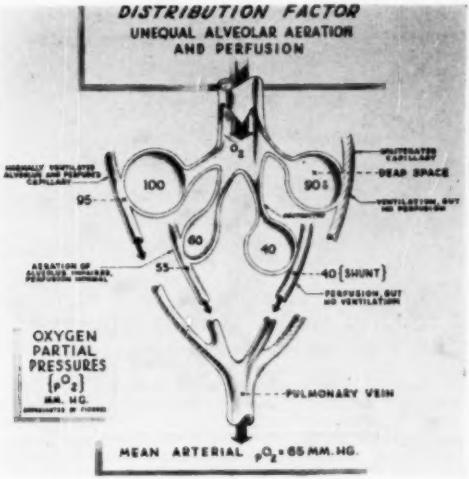
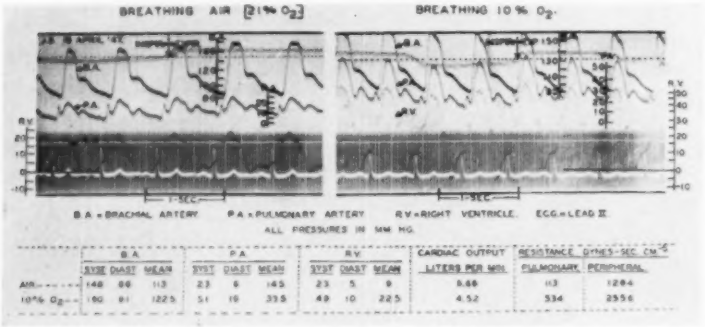


Fig. 1—A schematic diagram indicating the disturbed relationship between alveolar aeration and perfusion, as produced by pulmonary fibrosis, emphysema, retained secretions, bronchospasm, consolidation, pulmonary atelectasis or depression of respiration. Intermittent positive pressure breathing increases the alveolar pO_2 in those alveoli which have impaired aeration but are still perfused with blood. Intermittent positive pressure breathing has no effect on the oxygen transfer in alveoli which are perfused but nonaerated (unless some alveoli are opened up with the increased inspiratory pressure) or alveoli which are ventilated but not perfused. Elevating the inspired oxygen tension (pO_2) corrects for the unequal alveolar aeration, increases the arterial pO_2 to the normal range and compensates for small shunts due to perfusion with no alveolar aeration. In large shunts, however, such as those in the pulmonary circulation, even 100 per cent oxygen does not completely saturate the arterial blood.

impairment of the air circulation (loss of elasticity in the lung and narrowing of the bronchiolar lumina) so that although perfusion may be present, ventilation is inadequate or absent (Fig. 1). Alveoli which are perfused but nonaerated present circulatory pathways which act as small shunts and lower the arterial oxygen saturation (Fig. 1). The magnitude of such shunts can be calculated.[4,5] The blood flow to the alveolar capillaries may be obliterated to a greater or lesser extent, resulting in ventilation without perfusion, and the alveoli so involved are functional dead space. Hyperventilation can improve the situation only in alveoli poorly ventilated but still perfused with blood. The distribution factor is a common involvement in chronic pulmonary conditions with fibrosis, but this factor may occur with various degrees of obstruction to alveolar aeration as in atelectasis, consolidation of the lung, re-


BREATHING AIR (21% O2)
BREATHING 10% O2
B.A.
P.A.
R.V.
1 SEC
B.A. = BRACHIAL ARTERY P.A. = PULMONARY ARTERY R.V. = RIGHT VENTRICLE. ECG. = LEAD II
ALL PRESSURES IN MM. HG.

	B.A.			P.A.			R.V.			CARDIAC OUTPUT	RESISTANCE DYNES-SEC CM⁻⁵	
	SYST	DIAST	MEAN	SYST	DIAST	MEAN	SYST	DIAST	MEAN	LITERS PER MIN.	PULMONARY	PERIPHERAL
AIR	148	96	113	23	6	145	23	5	9	5.66	113	1264
10% O_2	150	91	1225	51	19	335	49	10	225	4.52	534	2556

Fig. 2—Photograph of pressure tracings showing the effect of low oxygen (10 per cent) breathing upon pulmonary artery blood pressure. Tracings of pressure in the pulmonary artery and in the right ventricle were taken through a double lumen catheter and recorded by a Hamilton manometer.[7] The maximal increase in pressure in the pulmonary artery was noted within five minutes after the low oxygen breathing was started. Some patients were observed for as long as twenty minutes on 10 per cent oxygen; the pulmonary artery pressure remained at the constant high level, but decreased to normal within five minutes after the low oxygen was removed.

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tained secretions or fluid and bronchospasm.

Acute hypoxia of short duration has been found to elevate pulmonary artery pressure in animals[6] and in man[7] (Fig. 2). Pulmonary vascular resistance was increased by acute hypoxia, but cardiac output in man as determined by the direct Fick method, was not increased.[7] The comatose patient should be promptly treated with oxygen to maintain a normal arterial oxygen saturation and thus prevent the increase in pulmonary vascular resistance which accompanies acute hypoxia and cyanosis. Cyanosis is a poor guide to the actual degree of hypoxia present. The recently perfected quantitative oximeter[8] provides a method for determining the arterial oxygen saturation which is more rapid and probably as accurate as the difficult and laborious Van Slyke method.[9]

Increasing the inspired partial pressure of oxygen (pO_2) may be adequate to produce a normal arterial oxygen saturation if there are no large areas of shunting such as occur in pneumonia with consolidation and in congenital defects. Maintenance of a normal arterial oxygen saturation by increasing the inspired pO_2 does not assure adequate removal of the carbon dioxide, because the minute volume ventilation

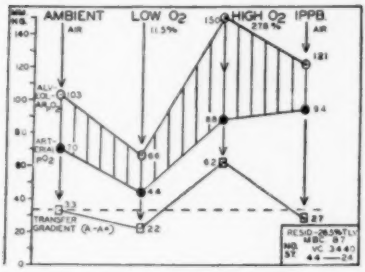

Fig. 3

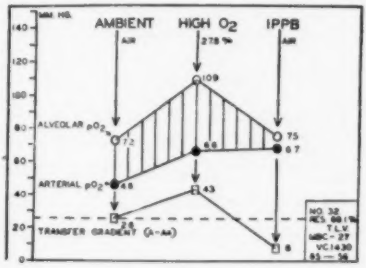

Fig. 4

Fig. 3—Diagram showing changes in alveolar and arterial pO_2 with low and high oxygen levels and intermittent positive pressure breathing in a patient with fibrosis but no pulmonary emphysema. The transfer gradient (the difference between alveolar and arterial mean pO_2) was greater than 30 mm.Hg. on ambient breathing. Note that the arterial pO_2 was increased with intermittent positive pressure breathing more than with high oxygen, although the alveolar pO_2 and transfer gradient were lower. Intermittent positive pressure breathing produces a more uniform aeration of those alveoli poorly ventilated by ambient breathing but still perfused with blood, and thus increases the arterial pO_2 more in proportion than the elevated alveolar pO_2 level of ambient breathing on high oxygen. Alveolar pO_2 calculated by the indirect method.[84]

Fig. 4—Diagram of changes produced in alveolar and arterial pO_2 with high oxygen breathing and intermittent positive pressure breathing in a patient with a far advanced degree of pulmonary emphysema. The transfer gradient (26 mm.Hg. on ambient breathing) was increased on high oxygen breathing and decreased to a normal level with intermittent positive pressure breathing, although the alveolar pO_2 was only 75 mm.Hg. with intermittent positive pressure breathing as compared to 109 mm.Hg. with high oxygen breathing, and the arterial pO_2 was not increased with the latter. Intermittent positive pressure breathing by increasing the aeration in the poorly ventilated alveoli on ambient breathing corrected the unequal alveolar aeration almost completely in this patient, and as there was very little perfusion difficulty, the transfer gradient assumed almost normal value.

may be grossly inadequate and many areas of the lungs poorly areated (as in atelectasis, pulmonary fibrosis, bronchospasm and pulmonary edema). That the use of intermittent positive pressure breathing provides a more uniform aeration of those alveoli which are poorly aerated but still perfused with blood is shown by the increase in the arterial oxygen saturation and decreased transfer gradient (Figs. 3 and 4).[10] The arterial pO_2 and oxygen saturation were increased more with intermittent positive pressure breathing on compressed air than with high oxygen (27.8 per cent) during ambient breathing (Figs. 3 and 4).[11]

Adequate removal of carbon dioxide depends on the minute ventilation and the uniformity of the alveolar aeration and perfusion. If the respiration is depressed, the carbon dioxide increases and the pH of the

TABLE I—OXYGEN BREATHING IN PULMONARY EMPHYSEMA (AMBIENT) ON A DEMAND SYSTEM

Case	*Residual Air Percent of Total Lung Volume*	*Arterial Blood*			
		On Air		*On 99.7% O_2 (10 min.)*	
		pCO_2**	pH	pCO_2**	pH
D.M.*	54.5	66	7.42	80	7.32
J.S.*	56.5	70	7.36	89	7.30
W.B.	61.5	47	7.46	64	7.39
L.M.	64.6	56	7.41	76	7.38

* Cardiac disease present.
** mm.Hg.

TABLE II—OXYGEN BREATHING IN OPERATIVE PROCEDURES

Thoracoplasty	*Arterial Blood*		
	*pO_2***	*pCO_2***	*pH*
Ambient Breathing, Air	98	37	7.48
During Anesthesia, controlled breathing—IPPB* type—with curare.	349+	69	7.32
Ambient Breathing, one hour postoperative—oxygen by B.L.B. mask.	320+	56	7.34

* Positive pressure only during inspiration-expiration at atmospheric pressure.
** mm.Hg.

arterial blood decreases (respiratory acidosis). The long-continued use of high oxygen levels, as 100 per cent oxygen in controlled anesthesia or in pulmonary emphysema (Tables I and II), lowers the arterial blood pH by elevating the arterial pCO_2 either through a decrease in ventilation or unequal alveolar aeration. Hydrogen ion concentrations as low as 6.90 have been observed in arterial blood during controlled anesthesia on patients receiving 100 per cent oxygen for three hours or more.[12] The arterial blood pH decreases gradually, and the longer the exposure on 100 per cent oxygen with the controlled anesthesia, the lower the pH. In patients with hypoxia as a result of inadequate ventilation the pCO_2 is elevated and the arterial blood pH decreased.

Patients needing artificial respiration or supplement to ambient breathing have an elevated arterial blood pCO_2, so that the further use of carbon dioxide in oxygen (as 5 or 7 per cent) is not physiologic.[13] The use of 5 per cent carbon dioxide only increases the acidosis of the apneic subject in need of artificial respiration. Studies on arterial blood before treatment have revealed decreased oxygen tension, arterial oxygen unsaturation, increased carbon dioxide content, increased pCO_2 and decreased arterial blood pH.[13] It is a popular misconception, largely due to the influence of Henderson,[14] that carbon dioxide mixtures are of value in the treatment of respiratory depression of asphyxia. Mixtures of carbon dioxide as high as 20 per cent have been advocated for use in artificial respiration on the assumption that a respiratory center too depressed to respond to 5 per cent carbon dioxide would respond to a higher concentration.[14] In the asphyxiated patient the blood carbon dioxide level is above normal so that the carbon dioxide no longer acts as a respiratory stimulant but in fact may be a depressant. In dogs subjected experimentally to severe, acute anoxia, 5 per cent carbon dioxide produced respiratory depression, and 15 per cent carbon dioxide produced even more profound respiratory and circulatory depression when administered in the same stage of hypoxia.[15]

Present concepts indicate that there is no rational basis for the use of carbon dioxide in asphyxia and that such a procedure is not only contraindicated but dangerous.[13, 15-19] Recently an experimental study was reported[18, 20] indicating that even in carbon monoxide poisoning, the addition of CO_2 to oxygen does not appear advantageous, oxygen alone being preferable. The Council on Physical Medicine and Rehabilitation of the American Medical Association and the American National Red Cross recommend that oxygen alone be used in resuscitators or inhalators instead of mixtures of oxygen and carbon dioxide.[21] It is of interest that in Fulton's recent (1949) "Textbook of Physiology"[22] the use of carbon dioxide gas mixtures in resuscitation is still advocated, although the present evidence reveals little rationale for the addition of carbon dioxide to gas breathing mixtures for use by patients with depressed breathing and hypoxia. Patients with chronic pulmonary disease and an advanced degree of impairment of pulmonary function with hypoxia may occasionally become delirious or unconscious when subjected to high concentrations of oxygen, a phenomenon attributable to the presence of a high pCO_2 with a respiration that is

being primarily maintained reflexively from the carotid sinus by the hypoxia stimulation; when the stimulation is suddenly removed by the high concentration of inspired oxygen the reflex control of respiration is decreased. The respiratory center has apparently become tolerant to carbon dioxide and thus the increase in arterial pCO_2 brought about by the decrease in ventilation while breathing the high oxygen mixture has no further stimulating effect. The decrease in arterial blood pH and the increase in the arterial pCO_2 appear primarily responsible for producing the delirious or unconscious state. I observed a patient at Bellevue Hospital with bullous emphysema and marked cyanosis who became unconscious within ten minutes after being placed on 100 per cent oxygen; when the patient was returned to air breathing with the appearance of cyanosis, consciousness returned. In such a patient, acclimated to chronic hypoxia of long duration, the concentration of oxygen breathed should be increased gradually.[23, 24] However, when a patient with far advanced bullous emphysema becomes acclimated to a high concentration of oxygen, discontinuance of the oxygen is extremely difficult.

Helium reduces the resistance of breathing air in and out of the lungs, and may relieve subjective dyspnea. The minimal helium-oxygen mixtures should be 70 per cent helium and 30 per cent oxygen, for if a 80 per cent helium and 20 per cent oxygen mixture is used, arterial blood measurements have revealed that in some cases the oxygen saturation* decreases (Fig. 5). The breathing may be easier with helium, but the oxygen saturation of the arterial blood may not be higher. The oxygen percentage in commercially supplied helium-oxygen tanks varies considerably; one tank of a supposedly 20 per cent oxygen and 80 per cent helium mixture delivered to our laboratory actually contained only 18.68 per cent oxygen, a lowering of sufficient magnitude to be significant to the patient with far advanced emphysema or depressed respiration. By reason of its great diffusibility, helium is a difficult gas to control, and gas mixtures containing helium are maintained at fixed concentrations only by the utmost care. Helium is also an inert foreign gas and the use of a 20 per cent oxygen and 80 per cent helium mixture after 10 minutes may lower the arterial oxygen saturation in emphysematous patients with adequate external minute ventilation. The use of from 30 to 40 per cent oxygen in the helium-oxygen gas mixture

* Determined from O_2 content and capacity on Van Slyke apparatus.[8]

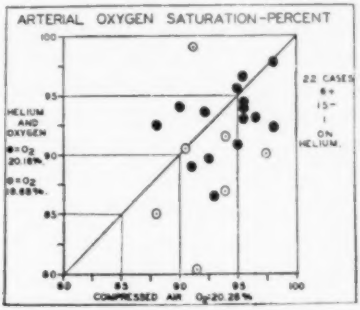

Fig. 5—Comparison of the resting arterial oxygen saturation while breathing compressed air with that obtained while breathing a helium-oxygen mixture through a demand regulator. These data were obtained on 22 cases of emphysema and fibrosis (most of the patients had anthracosilicosis). Note that in 10 cases the arterial oxygen saturation was slightly higher during the breathing of compressed air than during the breathing of the helium and oxygen mixture, although the oxygen percentage of both gas mixtures was essentially the same. When the arterial oxygen saturations of the 7 patients breathing the helium-oxygen mixture containing 18.68 per cent oxygen (this tank was supposed to contain 20 per cent oxygen and 80 per cent helium) were compared to those in the patients who breathed compressed air, there was a decrease in five cases, an increase in one case, and no change in one case. If a helium-oxygen gas breathing mixture is used, the oxygen should be increased to a minimum of 30 per cent.

appears to be the preferable procedure when helium is indicated to reduce breathing resistance in the dyspneic patient.

The question of irritation from the prolonged use of high oxygen concentrations may be a factor for consideration in the comatose patient. Observations made with the pneumatic balance respirator during long use of oxygen did not reveal any demonstrable irritating effect on the lung, as far as could be determined.[25] In one instance a postmortem examination of the lungs revealed no irritation of the alveoli or bronchi after three days of continuous intermittent positive pressure breathing through a tracheal catheter of 100 per cent oxygen by an apneic patient suffering from cerebral concussion following a blow on the head with a baseball bat. The greatest danger from the prolonged use of high oxygen concentrations in ambient breathing appears to arise from the decreased ventilation and reduction in uniformity of alveolar aeration, a condition which, in the presence of retained secretions, tends to promote the development of atelectasis in the more dependent portions of the lungs. The addition of a small amount of an inert gas (helium or nitrogen) is effective prophylaxis against the development of atelectasis,

which probably is the most serious complication of extended ambient breathing of 100 per cent of oxygen at atmospheric pressure. Substernal distress has been reported [26] in normal subjects breathing high oxygen concentrations for twenty-four hours. Breathing dry oxygen during a simulated ascent to high altitude in a low pressure chamber may irritate the throat, producing coughing and mild substernal discomfort somewhat similar to chokes (a manifestation of aeroembolism). Since the inspired pO_2 is elevated to a very high level with 60 per cent oxygen (Barometric pressure -47 mm.Hg. $\times$ 60 per cent = effective inspired pO_2), it is unnecessary to use 100 per cent oxygen in ambient breathing in comatose patients to saturate the arterial blood. The use of from 60 to 70 per cent oxygen mixture will protect against atelectasis and yet provide a high enough inspiratory pO_2 for maintenance of good arterial oxygen saturation in most cases, but such a mixture does not necessarily provide adequate ventilation.

Common methods of increasing oxygen tension and saturation in the arterial blood include the use of: the oxygen tent, the nasal catheter, the continuous flow oxygen system with a mask (BLB and OEM) and the demand oxygen system (Mine Safety Appliance and Scott Aviation Corporation). The demand oxygen system (unless provided with a diluter arrangement on the regulator) provides essentially the same oxygen concentration to the mask as in the supply tank of compressed gas; hence the demand system should not be used continuously on comatose patients by ambient breathing over prolonged periods of time unless the tank mixture has an inert gas dilutant such as nitrogen or helium. The Drinker type respirator can be used to give artificial respiration with oxygen therapy provided by a catheter, mask or demand system. The prolonged use of the Drinker type respirator predisposes to the formation of atelectatic areas in the lungs and loss of muscle tone, often complicated by the development of bronchopneumonia and pulmonary edema. Bennett[27] has designed a cycling valve to supplement the Drinker respirator with intermittent positive pressure breathing, a procedure that has decreased complications in bulbar poliomyelitis patients and has saved lives.

Intermittent positive pressure breathing (IPPB) consists of an active inflation of the lungs during inspiration under positive pressure from a cycling valve with a maximal peak pressure at the mouth adjustable from 0 to 30 centimeters of water. After the valve cycles, expiration

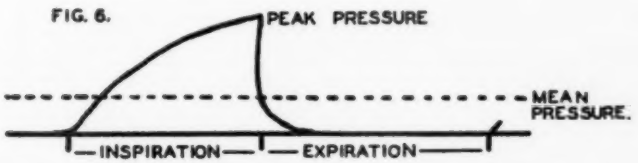

Fig. 6—Mask pressure curve illustrating the time-pressure relationship previously described and discussed as type III.[28] The type III mask pressure curve is asymmetrical, with a pressure gradually increasing during inspiration and rapidly dropping to atmospheric level early in expiration. Expiratory time equals or exceeds inspiratory time, and the inspiratory mean mask pressure is high as compared to the expiratory mean mask pressure, which is very low (most of the mean mask pressure for the entire respiratory cycle being exerted during the inspiratory phase). This type of mask pressure curve (type III) provides a peak pressure which is effective in overcoming breathing resistance and maintains adequate ventilation with a minimal mean mask pressure without decreasing cardiac output in man.[25, 28]

occurs as a passive deflation produced primarily by the elasticity of the lungs and the wall of the chest. The cycling of the respirator valve follows the patient's pattern of breathing.

Factors to be considered in using IPPB are related to the shape and duration of the mask pressure applied at the mouth; namely, the time relationship of inspiration and expiration, the cycling rate and the magnitude of pressures applied (maximal, minimal and mean). The most desirable type of pressure to apply to the mask or through an intratracheal tube is a mask pressure curve that is asymmetrical, gradually increasing during inspiration and rapidly dropping to atmospheric level early in expiration. Expiratory time is equal to or greater than inspiratory time, and most of the mean mask pressure is exerted during the inspiratory period (Fig. 6), previously described as type III mask pressure curve.[28] This type of intermittent positive pressure breathing provides a high peak mask pressure effective in overcoming breathing resistance, yet the mean mask pressure for the entire respiratory cycle is low. No deleterious effects on the pulmonary circulation (Fig. 7), either on blood pressure or cardiac output,[28] were noted when the type III IPPB was used. IPPB has been found useful in the treatment of acute pulmonary edema,[29] in the maintenance of adequate ventilation in depressed respiratory states,[13] in giving breathing exercise with more uniform distribution of simultaneously administered aerosols,[30] in promoting bronchial drainage,[31] and in providing more uniform alveolar

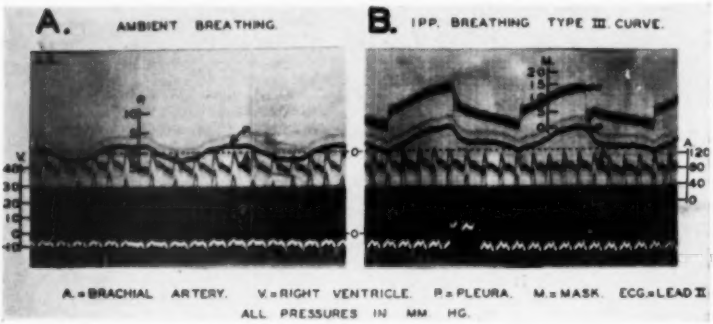
A. AMBIENT BREATHING
B. IPP. BREATHING TYPE III. CURVE.
A = BRACHIAL ARTERY. V = RIGHT VENTRICLE. P = PLEURA. M = MASK. ECG = LEAD II.
ALL PRESSURES IN MM. HG.

Fig. 7—A photograph of pressure tracings during ambient and respirator breathing, using type III mask pressure curve on an essentially normal subject. (A) Pressure tracing during ambient breathing. From above downward: pleural, brachial artery and right ventricle. (B) Pressure tracing while breathing with the respirator. From above downward: mask, pleural, brachial artery and right ventricle.

From *Am. J. Physiol.*, 1948, *152*:162. (*Reprinted by permission*)

aeration,[3] with protection against the development of atelectasis.[27] No apparent advantage has been found from the use of negative pressure in part of the respiratory cycle,[13] and the potential danger of negative pressure in patients with threatened pulmonary edema would seem to make IPPB the method of choice.

The use of intermittent positive pressure breathing for prolonged periods does not produce distention of the lung or increase the amount of residual air even in patients with a far advanced degree of emphysema.[32] The instantaneous flow rate of the respiratory appliance may be too low to meet the needs of the acute asthmatic and cardiac patient (Fig. 8).[29]

The Pneophore* is an automatic, pressure-sensitive, cycling device for giving IPPB for therapeutic use. This apparatus provides adequate minute ventilation volumes even in apneic subjects, and may be combined with a nebulizer for the simultaneous administration of an aerosol during the IPPB.[30] The nebulizer attachment on the Pneophore makes a valuable emergency apparatus for giving adrenergic drugs with oxygen in depressed respiratory states because the intake of the drug from the large pulmonary absorptive area is rapid. Since the in-

* Manufactured by Mine Safety Appliance Co., Pittsburgh, Penna.

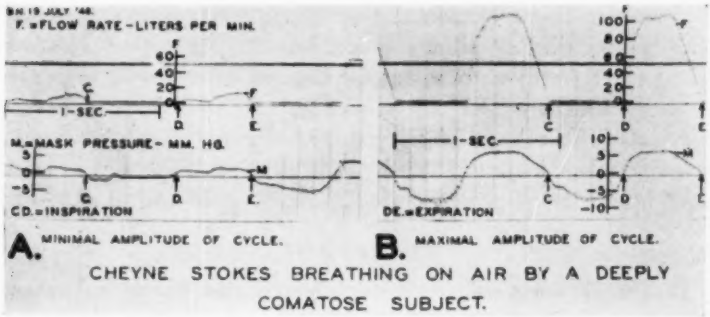
F. = FLOW RATE - LITERS PER MIN.
1-SEC.
M. = MASK PRESSURE - MM. HG.
CD. = INSPIRATION
DE. = EXPIRATION
A. MINIMAL AMPLITUDE OF CYCLE.
B. MAXIMAL AMPLITUDE OF CYCLE.
CHEYNE STOKES BREATHING ON AIR BY A DEEPLY COMATOSE SUBJECT.

Fig. 8—A photograph of a tracing of instantaneous flow rates and mask pressure curves on a patient with Cheyne-Stokes breathing. (A) During period of minimal breathing, the maximal instantaneous flow rate was approximately 10 liters per minute. (B) During period of maximal breathing, the instantaneous flow rate exceeded 100 liters per minute. The flow capacity of respirator apparatus must be greater than the maximal instantaneous flow rate of the patient at all times in order to prevent the development of a greater negative pressure during inspiration with subjective dyspnea in the conscious subject.

From *J. Aviation Med.*, 1947, *18*:417. (Reprinted by permission)

stantaneous flow rate is approximately 50 to 60 liters per minute, this apparatus should not be used on acute decompensated cardiacs or asthmatics. The Demand Pneophore has a demand regulator to provide additional flow capacity in case the instantaneous flow rate of the "Burns" type cycling valve[33] used on the standard Pneophore is inadequate. The Demand Pneophore is suitable for use on all types of patients. The Bennett type cycling valve* based on flow characteristics rather than pressure[25] is very satisfactory for administering IPPB, especially for the combined use with the nebulizer in giving aerosols. This apparatus provides high instantaneous flow, has an atmospheric mean expiratory pressure at the mouth and is easy to clean and maintain because there is no rebreathing through the cycling valve. The cycling valve follows the patient's pattern of breathing and the instantaneous flow rate is high (well over 100 liters per minute). Operation of this unit is economical, as oxygen may be used to enrich the compressed air as indicated. This apparatus is useful in treatment for all types of depressed breathing, including postoperative anesthetic cases, because it simultaneously increases ventilation and inspired oxygen, blows off car-

* Manufactured by J. J. Monaghan Company, Inc., Denver, Colorado.

bon dioxide and protects against atelectasis.

Electrocardiographic studies made after prolonged periods of IPPB with 100 per cent oxygen and potent bronchodilator drugs (Vaponefrin, Isuprel) revealed no significant changes. However, in several instances when compressed air was used instead of 100 per cent oxygen, depression of the RS-T segments and inversion of the T waves were noted with the drugs mentioned.[31] The electrocardiogram was not altered by the use of neosynephrine in the nebulizer with the IPPB.

Conclusions

1. The two essential factors for consideration in the maintenance of normal respiratory gas exchange in comatose subjects are: (1) an inspired pO_2 of sufficient magnitude to saturate the arterial blood and (2) adequate ventilation to wash out the carbon dioxide effectively, thus preventing the development of respiratory acidosis. Administration of high concentrations of oxygen controls the first factor in most cases, but on ambient breathing alone the second factor is often inadequately handled.

2. Unequal alveolar aeration and perfusion (the distribution factor) produced by fibrosis, bronchospasm, atelectasis, consolidation, retained secretions or depressed respiration or any combination of these, usually constitute the major impairment present in the comatose patient in need of oxygen therapy.

3. Acute hypoxia increases pulmonary vascular resistance and increases the load on the right side of the heart.

4. Carbon dioxide should not be used with the oxygen in respirators, resuscitators or insufflators for treating asphyxia because the use of 5 per cent carbon dioxide only increases the acidosis in apneic subjects in need of artificial respiration.

5. The preferred minimal oxygen-helium mixture is 30 per cent oxygen and 70 per cent helium.

6. The development of atelectasis appears to be the greatest danger from the prolonged use of high oxygen concentrations during ambient breathing, but repeated intervals of intermittent positive pressure breathing (IPPB) appear to offer effective prophylaxis.

7. For prolonged use by ambient breathing in comatose patients, 60 to 70 per cent oxygen mixed with an inert gas protects against atelectasis and in most cases saturates the arterial blood adequately, however,

this mixture does not necessarily provide adequate ventilation. A lowering of the arterial blood pH below 7.35 reveals the presence of severe uncompensated respiratory acidosis due to an inadequate minute ventilation volume.

8. IPPB provides more uniform aeration of alveoli perfused with blood, but previously poorly aerated, increases minute ventilation volume with maintenance of adequate ventilation during respiratory depression, lowers arterial pCO_2, protects against atelectasis, promotes bronchial drainage and provides a useful method in the treatment of acute pulmonary edema.

9. IPPB can be administered without alterations of cardiac hemodynamics (lowering blood pressure, or cardiac output). It provides adequate ventilation in the comatose patient so that respiratory acidosis is readily controlled. Several types of respirators for producing IPPB are described. The instantaneous flow rate of these devices should be at least 100 liters per minute.

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OUTLINE OF THE USE OF RESPIRATORS AND OF OXYGEN IN POLIOMYELITIS

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I. First, prevent, if possible, the necessity for the use of respirators or oxygen, by maximum rest for the patient and minimum handling. Rest and reassurance are of importance.

II. Determine nature and causes of the breathing difficulty

Possible causes:

A. Disturbances of breathing mechanism
   1. Tightness of muscles of breathing
   2. Weakness of muscles of breathing
   3. Failure of respiratory center

B. Interference with O_2 and CO_2 exchange
   1. In pharynx
      a. Accumulation of fluids due to inability to swallow
      b. Paralysis of tongue
   2. In larynx
      a. Abductor paralysis of vocal cords
      b. Spasm of glottis
   3. In trachea and bronchi
      a. Accumulation of mucus from bronchitis
      b. Inhalation of saliva from pharynx
      c. Inhalation of vomitus
   4. In lungs
      a. Atelectasis
      b. Pneumonia
      c. Pulmonary edema
   5. In central nervous system; edema

C. Contributory factors
   1. Panic and hysteria
   2. Sedation
   3. Anemia
   4. Air swallowing
   5. Vomiting
   6. Fatigue

III. Remove causes or aggravating factors, including:
Postural drainage, suction for pharyngeal fluids
Calming the panicky
Encouraging natural sleep without sedation
Transfusion if necessary
Attention to the bowel and bladder

IV. Give oxygen comfortably—preferably before there are definite signs of need.

V. Dehydrate with 10 per cent glucose intravenously and do not flood patient with fluids

VI. Indications for artificial respiration. (Opinions differ.)
Vary according to type of case:
a. Pure spinal—certainly if there is cyanosis
b. Pure bulbar—usually only in extremis
c. Mixed bulbar and spinal—keen clinical judgment and experience necessary

VII. Types of artificial respiration available
1. Tank respirator
2. Chest respirator
3. Rocking bed
4. Manual
5. Phrenic stimulation

VIII. Essential precautions in use of tank respirators
A. Spinal cases
1. Constant observation without disturbance
2. Adequate oxygen supply
3. Occasional change of position
4. Occasional change of pressure
5. Early weaning from respirator and early breathing exercises
6. Gradual decrease of pressure if possible and weaning to rocking bed

B. Bulbo-spinal cases
1. Establish clear airway—nose and throat consultation
2. Slower to put in respirator
3. Postural drainage, prone or side position
4. Adequate oxygen supply
5. Watch blood pressure—neosynephrine by hypo if falling

C. Bulbar

Respiratory center involved with irregular, incoördinate breathing, prescribe:

1. Caffein
2. Diaphragmatic respiration, by rocking bed or phrenic stimulation

IX. Tracheotomy in polio

A. Indications

1. Bilateral abductor paralysis of larynx
2. Inability to keep airway clear
3. Progressive hypoxia, not otherwise correctible.

B. Advantages

1. Easy removal of secretions
2. Ability to do bronchoscopy through wound, if proper oxygen attachment is available
3. Easier maintenance of adequate oxygen tension
4. Easier treatment of pulmonary edema with positive pressure
5. Easier to care for patient

C. Disadvantages

1. Operation an ordeal to patient who needs rest
2. Possible complications
3. High mortality of tracheotomy in poliomyelitis
4. Tube narrows the airway
5. Tube increases intratracheal secretions
6. Makes adequate oxygen administration difficult unless proper attachment is available

D. Indications insufficient in themselves

1. Inability to cough
2. Inability to swallow
3. Moderate laryngeal paralysis
4. Pulmonary edema
5. Atelectasis

E. Personal opinion: Tracheotomy should be avoided if in any way possible.

SECTION ON MICROBIOLOGY

JANUARY 18, 1950

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STUDIES ON VIRULENCE OF TUBERCLE BACILLI

a. Experimental analysis of the virulence of tubercle bacilli
Gardner Middlebrook (by invitation)
The Rockefeller Institute for Medical Research

b. A component of tubercle bacilli concerned in their virulence
Hubert Bloch (by invitation)
The Public Health Research Institute of the City of New York, Inc.

c. The application of virulence studies to the BCG problem
René J. Dubos
Cynthia H. Pierce (by invitation)
Emanuel W. Suter (by invitation)
The Rockefeller Institute for Medical Research

FRANK L. HORSFALL, JR.
Chairman
HARRY MOST
Secretary

The Experimental Analysis of Virulence of Tubercle Bacilli

GARDNER MIDDLEBROOK*

The purpose of this symposium is to acquaint you with recent experimental observations concerning the virulence of tubercle bacilli and to summarize the theoretical as well as the experimental background on which these observations have been based. It will be evident, I am sure, from Dr. Dubos' talk, that the problem with which we are concerning ourselves tonight has immediate implications for problems of vaccination.

The background of these studies may be of as much interest as the studies themselves. They are based upon an explicit, rational procedure for studying infectious disease in terms of the virulence of the pathogen. This will be the central theme of my talk.

Let us first define our terms.

"The Nature of Virulence" was the title given to a recent symposium.[1] An examination of the communications abstracted from that symposium reveals the general state of confusion concerning the use of the term virulence in microbiology. The problem is, I think, a semantic one, based upon the fallacy of accepting a word as something magically born from the head of Zeus and of looking for a concrete thing or phenomenon with which to identify the word. In highly evolved fields of scientific inquiry this form of question: "What is the Nature of Something?" and the resulting controversies which only confound understanding rarely appear. It is understood that such problems can be resolved by the employment

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of arbitrary definitions which are only required to be useful as means of communication in operational terms.[2]

Inasmuch as it has not been possible for us to find in the literature generally accepted and useful definitions of the terms virulence and pathogenicity, it appears essential to formulate clear-cut definitions for these terms before discussing tonight's topics.

I propose in this talk to limit the term pathogenicity, as applied to living agents, to the following meaning: pathogenicity is that general attribute of a strain of microörganism or general class (usually a subspecies) of microörganism which characterizes it as being able under a specified set of conditions to produce disease by multiplying in or on some living host. Disease is understood, of course, to mean either obvious death of tissues or gross impairment of biological function. A strain or class of microörganisms may be said, in general terms, to be pathogenic if it has pathogenicity for any host, and, conversely, a strain or class may be said to be non-pathogenic (i.e., saprophytic or parasitic but non-pathogenic), if it has no known pathogenicity for any host. And also, a strain or class which is pathogenic for one host may be said to be specifically non-pathogenic for another. Pathogenicity concerns the relations of parasite A and hosts x, y, z, etc.

By virulence I mean that measurable property of a particular strain of microörganism by which it can be distinguished quantitatively from other similar strains of the same class, or from "variants" of the same strain, in respect to pathogenicity for one specific susceptible host. Thus, in contrast to pathogenicity, virulence concerns comparative relations of similar strains A, B, C, etc. and host x. It implies degree of pathogenicity of a specific strain for a particular host in comparison with similar strains of the same class for the same host, tested under the same set of experimental conditions. Thus, variations in virulence imply inheritable variations in the strain of microörganism such as occur in so-called dissociation and which are probably genetic in character. These variations ideally involve identical variations in every individual cell in the strain as tested in the same host, without differences in the numbers of living microörganisms introduced into the test host or other changes in the experimental conditions, such as growth medium or ages of the cultures of the strain compared. In summary then, the term "virulence" is equivalent to the phrase "degree of pathogenicity for a specified host." It is, of course, imperative for an understanding of the concepts to be entertained here that variations in the host, though they are emphatically of as great import for a general view of host-parasite relationships as variations in the parasite, be considered as having no relevance to virulence: a constant, specific, susceptible host is an essential assumption in any problem of virulence. Variations in the host being well controlled or, in the words of L. J. Henderson, "other things being equal (which they never are in practice)," virulence can be fruitfully studied.

Needless to say here, it is usually possible to control all such variables by employing a statistically significant number of individual hosts in the testing of pathogenic strains, and it will be seen that the term virulence defined in these respects has usefulness at certain levels of analysis of many types of host-parasite relationship.

I should remind you that no single property of a parasite can be considered a "cause of virulence." Obviously many properties, few of which are ever actually identified, are essential for the manifestation of virulence by a microörganism. Those strains of pneumococcus which synthesize well-developed capsules and yet are incapable of causing disease serve as the classical illustration of the fact that no one property or component of a parasite is sufficient for the manifestation of virulence, though it may be essential. This leads us to the scheme of analysis of infectious disease which served as a background for the work to be described tonight.

A CONCEPTUAL SCHEME OF EXPERIMENTAL ANALYSIS

The succession of discoveries that immunization of animals with water soluble toxic products of pathogenic diphtheria, tetanus, and certain (erythrogenic toxin producing)

streptococcus cultures could confer high degrees of acquired resistance against the diseases caused by those microbes led to almost tireless search for similar poisonous substances in the artificial cultures of other pathogenic microbes with the view to inducing a similar state of immunity against them. Then interest was revived for the early established use for vaccination of virulent, but specifically non-pathogenic, strains (cowpox vaccination against smallpox in human beings) and of living attenuated or avirulent strains of the same organism (Pasteur's use of attenuated anthrax cultures). Calmette's experiments with BCG emphasized the earlier observations.

These accents in the practical field of immunization against microbial infections soon echoed and now resound in the laboratory of the microbiologist who became interested in variation in microörganisms as a theoretical study in general biology without any necessary relation to the pathogenesis of infections. Yet there appeared during the past thirty years studies of the relationship of the capsular polysaccharides of pneumococci to immunization against, and the manifestation of virulence in, this class of pathogen. These investigations established several important points pertinent to our discussion: the manifestation of virulence does not necessarily depend only upon the production by a microörganism of a substance with lethal toxicity, because, although the pneumococcus might produce a toxic substance as it multiplied *in vivo*, the loss of its ability by dissociation (genetic variation, in all likelihood) to produce an apparently non-toxic surface polysaccharide, inability to accumulate a sufficient amount of the substance at the surface of each bacterial cell, or combination of this material with specific antibody, all render the pathogen unable to manifest virulence. Another fact relevant to this review is the observation that there are strains of pneumococci which are apparently avirulent and yet capable of inducing upon injection into animals high degrees of acquired resistance against virulent strains, because of their production of *small* amounts of capsular polysaccharide, sufficient to elicit type-specific "protective" antibody, but insufficient to allow a clearly detectable manifestation of virulence. In other words, variation and virulence are not necessarily of an all or none nature.

Analogous to this information concerning the pneumococcus are the more limited observations made in studies of other classes of bacterial pathogens. These facts have, on the one hand, given the experimental basis for a new interpretation of Pasteur's and subsequent use of "avirulent" variants for immunization against virulent strains. On the other hand, their pertinence to the problem of the relation of properties of the bacterial cell to the pathogenesis of disease is further established by the following correlative generalization for which there are thus far no recognized exceptions: antibodies (serum globulins) which are protective against infectious disease are always directed against antigenic components of the microbial cells which are essential in some respect or another for the manifestation of virulence; for when these antigens, and these antigens alone, are lost in dissociation (hereditary variation), virulence also is lost.

With a broad view of this wealth of experimental observations, Dubos[2] was led to state that it is not essential to exert a non-specific, lethal effect on a pathogenic microörganism in the treatment or prevention of infectious disease, but that it is merely necessary to interfere with the operation of only one of several properties of the parasite essential for its pathogenic career. Carrying this conceptual scheme further, to the point of explicit formulation of a rational method of analyzing infectious disease, appeared to offer practical as well as theoretically significant results.

The operational steps in this organized method presented themselves as follows:

1. Obtain a relatively stable virulent strain of the pathogenic parasite.

2. Select by the use of any of the many techniques now available (radiation treatment, ageing of cultures, dissociation by colony isolation, heterologous animal passage, etc.) variant cultures of the parent pathogen which have lost their virulence (for the host with which one is concerned).

3. Compare the avirulent variant strains

(dissociants) with the parent virulent strain by techniques which will allow quantitative as well as qualitative analysis in an effort to identify at least one physiological change (immunochemical, biochemical, etc.) which has taken place simultaneously with the change in virulence. This identification of a virulence property is assured by the demonstration that, on the one hand, the property is possessed by all virulent strains of the same class and that, on the other hand, those variant strains which lack it are avirulent.

4. Analyze the pathogenesis of the disease caused by the pathogen in terms of this specific difference between virulent and avirulent variant strains, or in terms of the special property of the virulent variants.

5. And, finally, depending upon the nature of this difference and its particular role in the pathogenesis of the disease, aim at the prevention* and treatment of the disease in terms of this difference.

Examination of the literature on variation and virulence of bacteria, fungi and protozoa reveals the following three generalizations.

First, independent variations in specific properties of strains of microörganisms which reproduce asexually occur much more often than simultaneous variations in several properties. Were this not the case, it can be imagined, how inappropriate and irrational the above scheme would be. Second, marked and easily recognizable variations in certain properties (antigenic, biochemical, etc.) of bacterial strains may occur without change in virulence. And third, the manifestation of virulence, as emphasized above, depends upon the operation of many properties of any one microörganism; thus, there is usually a wide choice as to what essential property is to be experimentally pursued—which, of course, can be decided only in terms of the special purpose of the pursuit. From the practical standpoint of prophylaxis or therapy of infectious disease, a property which promises to be most amenable to attack with the well-established methods would naturally be selected first for thorough investigation. It is perhaps not necessary to state that limitation of endeavor at this level, without a search for new methods suggested by the nature of the role played by the essential property in the host-parasite relationship, would lead to undesirable stagnation.

Although the plan of experimental analysis just described may seem obvious—simple and logical—it must be stressed that in all instances where effective methods of immunization have been developed, successful immunization has been achieved before actual identification of any of the properties of the pathogen which are essential for the manifestation of virulence. In point of fact, successful immunization has itself often allowed elucidation of the properties of the pathogen essential for virulence. Although there has been a general awareness of the significance of virulence studies for problems of immunization, this rationally formulated plan had not been explicitly employed in the analysis of any infectious disease before its use in the studies of tuberculosis which we are reviewing tonight.

The direct application of the steps of analysis based upon the theoretical scheme which I have presented is straightforward for the study of host-pathogen relationships in which the pathogen is a microörganism readily cultivatable *in vitro*. An avirulent variant can often, in such instances, also be grown *in vitro*. It is at this level that such a study is to be initiated until evidence indicates that the significant difference between the virulent and avirulent variants is manifest only under conditions for multiplication existing *in vivo* and not yet imitable *in vitro*. On the other hand, in the case of virus and rickettsial infections the application of this conceptual scheme would be necessarily more challenging experimentally but perhaps approachable even at the present time in those instances in which marked loss of virulence occurs on heterologous host passage in the case of plant as well as animal viruses. More thorough discussion here on these points would be out of place, but the pertinency of this method of analysis to the several types of host-pathogen relations is plain.

* Ecological and epidemiological considerations in the prevention of disease are purposely avoided here as they have no essential relevancy at this limited level of analysis of host-pathogen relationships.

VIRULENCE OF TUBERCLE BACILLI AND TUBERCULOSIS

Although it is nearly a quarter of a century since the pioneer work of Petroff and his associates[4] on dissociation of tubercle bacilli with the isolation of "pure" avirulent variant strains of mammalian (and avian) types, extension of these studies has been slow. More recently, however, the gradual emergence and explicit formulation of the conceptual scheme of relations between the virulence of pathogens and the pathogenesis of infectious processes, as outlined above, has stimulated novel investigations of tuberculous infection and disease.

The first and second steps of the analysis had been accomplished by several groups of investigators subsequent to Petroff's early observations, but many problems presented themselves relating to techniques of cultivation, standardization and control of infective inocula, the use of that convenient experimental host, the mouse, the evaluation of the mouse as a host in the study of the virulence of the parasite, and the probability that observations on that host would reveal significant information relating virulence and the disease, tuberculosis, as it occurs naturally in other hosts, especially in man.

Certain biological properties of mammalian type (human and bovine) tubercle bacilli, it soon became evident, made them suitable for virulence studies. Most strains were easily cultivated *in vitro*, both the virulent and the avirulent variants, especially in the media newly devised by Dr. Dubos and his associates. Many strains were quite stable with respect to virulence, and virulent (H37Rv) and avirulent (H37Ra) variants of the same well-known strain appeared to be especially appropriate pure cultures with which to begin the third step of analysis.[5] The pathology of the disease, although markedly different in different hosts, did not vary qualitatively in its several aspects in the mouse any more than in the guinea pig or other hosts with different strains of the same subspecies of tubercle bacilli (e.g., human type), provided that equal doses and the same route were used for infection. Various techniques of testing virulence, such as using different routes of inoculation, did not reveal different orders of virulence of several strains of the same subspecies of tubercle bacilli in the mouse; and the order of virulence of strains of the same subspecies appeared to be approximately the same in races of mice which differed widely with respect to susceptibility; this order, furthermore, proved to be identical with that which had been observed for the same strains in the guinea pig and, probably, in man.[6] This latter circumstance favored the possibility that the properties of human type tubercle bacilli which condition virulence are, at least qualitatively, the same for many hosts.

Two additional important problems relating to the pathogenesis of tuberculosis were considered in these investigations. One is concerned with the possible direct relevance to virulence of the hypersensitivity to tuberculin which develops during the course of the disease in many susceptible hosts. It was clear that, although hypersensitivity certainly plays a role in the pathology—one may say, the pathogenesis—of tuberculosis in certain hosts, including man, it is not involved in the variations in virulence of tubercle bacilli with which we have become acquainted. This was demonstrated by several facts:

1. The virulent and avirulent variants with which we are acquainted are equally active producers of tuberculin *in vitro*.[7]

2. Both, when killed, are effective in inducing the state of hypersensitivity to tuberculin.

3. The avirulent variants with which we are concerned are not capable of establishing progressive disease in animals which have been previously rendered hypersensitive.

4. The bacilli of the completely avirulent variant strains multiply little, if at all, even within the first few days after inoculation into susceptible hosts, in contrast to the unharnessed multiplication of virulent tubercle bacilli—that is, before hypersensitivity appears.[8] In this connection I would emphasize another point of importance in the differential properties of our virulent and avirulent variants. They behave differently in the susceptible host even before histologic lesions are recognizably charac-

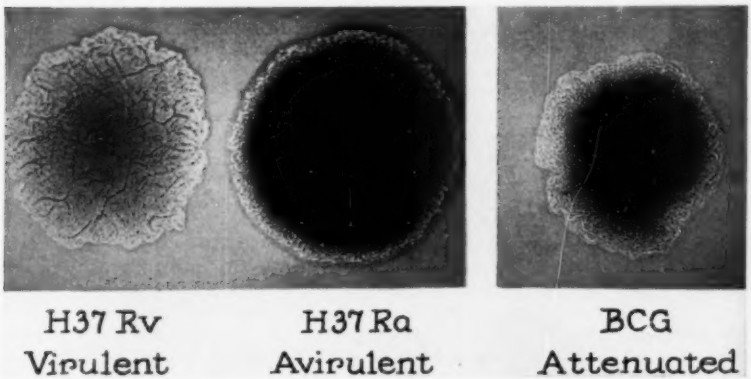


Fig. 1
H37Rv (virulent) and H37Ra (avirulent) X97

Fig. 2
BCG 317 (attenuated) X97

These photomicrographs illustrate the colonial morphological differences between typical strains of mammalian tubercle bacilli possessing different degrees of virulence.

Fig. 1 shows two colonies growing side by side on the surface of an agar medium (oleic acid-albumin medium). To this medium was added before inoculation 0.004% of a non-ionic, non-toxic wetting agent, Triton A20, which, it has been shown (Dubos, R. J. and Middlebrook, G. *J. Exper. Med.*, 1948, *88;* 81), disperses the bacilli of non-cord-forming, avirulent variants of mammalian strains, but does not inhibit the cord formation of virulent strains. Clearly evident are the serpentine pattern of the colony of the virulent strain and the non-oriented, almost "smooth" structure of the avirulent variant strain's colony.

Fig. 2 shows the morphological appearance of a colony of an attenuated but not completely avirulent BCG strain (317); it is evidently intermediate in structure between the fully virulent strain and the non-cord-forming avirulent strain illustrated in Fig. 1.

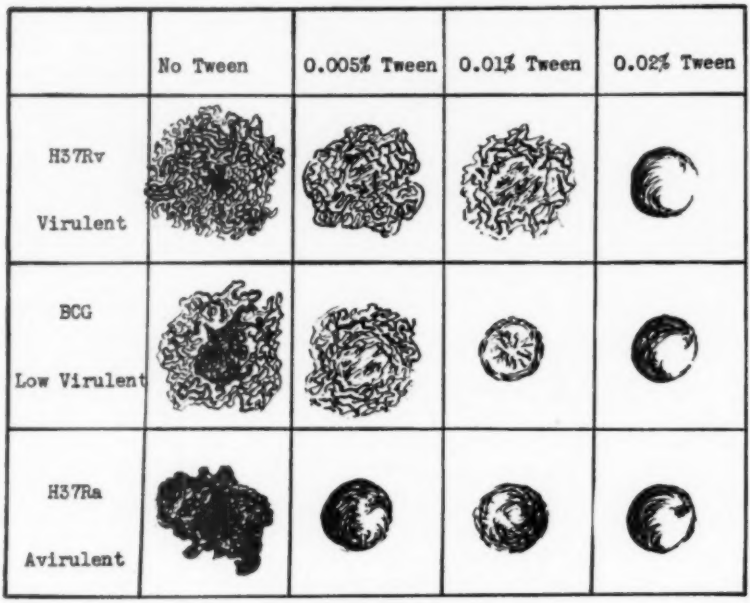
The use of the lipophilic wetting agent, Triton A20, facilitates visualization of colony differences which are, nonetheless, visible on the same medium without this adjuvant.

teristic of progressive tuberculous infection. This indicates that at least one of the most important properties of the virulent pathogen in the host-pathogen relationship in tuberculosis manifests itself before the establishment of the characteristic anatomical lesion. This assumption, it will become evident to you this evening, greatly influenced the types of questions which we asked and the particular experiments which were performed.

The other important problem which we faced was the question as to whether the significant biological differences between virulent and avirulent variants would be manifest as they were cultivated *in vitro*. An abundance of previous observations, it is true, had shown that, unlike acquired resistance in anthrax and perhaps in some other infectious diseases, there is no convincing evidence that actual infection with virulent or attenuated tubercle bacilli confers a type of acquired resistance against tuberculous infection or disease which is qualitatively different from immunity conferred by virulent tubercle bacilli grown *in vitro* and killed by various techniques. Certainly then, tubercle bacilli, multiplying *in vitro*, do produce at least some of the antigenic chemical components which they produce *in vivo*—as far as protective antigens are concerned. There was, however, no assurance that the differences between our virulent and avirulent variants would have any bearing on acquired resistance as we know it in tuberculosis.

At any rate, with purposeful disregard of hypersensitivity at this stage of analysis, and confidence, perhaps insufficiently assured, in artificial cultures of tubercle ba-

Representation of Effect of "Tween 80" on Colony Morphology of Typical Mammalian Strains



SCHEMA

(Acknowledgment: From The Journal of Experimental Medicine, Vol. 82, p. 181, 1947.)

cilli, study was aimed at the identification of at least one property of the virulent variant of the H37 strain which was consistently lacking in the avirulent variant of the same strain.

It was soon observed[9] that when the two strains, H37Rv (virulent) and H37Ra (avirulent), were grown on the surface or in the depth of many types of artificial media, there was a consistent microscopically demonstrable difference between the two strains in their morphological properties. The avirulent variant, H37Ra, was observed to present a non-oriented microscopical arrangement of bacilli in clumps. On the contrary, the virulent variant, H37Rv, grew in an impressively oriented pattern of what I call "cords" of bacilli, in which the rods arrange themselves in parallel along the long axis of the cord. It is interesting that Robert Koch,[10] in one of his first papers on the cause of tuberculosis observed, and even pictured, the cord pattern of growth of virulent tubercle bacilli. Needless to say, however, he did not attach any special significance to it (Figure 1).

As I have pointed out earlier, a property significant for virulence must satisfy the following requirements: it must be possessed by all the virulent strains of the same class; and, all strains which lack it must be avirulent.

Therefore, extension of these observations on morphology was made to other eugonic strains of tubercle bacilli, and thus far, it has invariably been noted that those var-

iants of eugonic mammalian strains which fail to form cords are avirulent, and that all virulent strains form cords. In addition, the BCG strains of which Dr. Dubos will speak, afford examples of the intermediate group of tubercle bacilli—intermediate both in respect to virulence and to cord formation (Figure 2). They form an intriguing group with which much work remains to be done, especially with respect to the refinement of quantitative methods for testing virulence. I venture the opinion that the BCG group of strains of mammalian tubercle bacilli, as represented by the cultures which I have studied, is analogous to those pneumococcus variants, mentioned before, which produce small amounts of capsular polysaccharide adequate to allow them to manifest a slight virulence in susceptible hosts, but insufficient to allow them to cause severe infection or disease.

A correlation was thus established between the virulence of mammalian tubercle bacilli and their tendency to orient themselves according to a particular pattern during multiplication in many types of artificial media. Although this correlation gives no direct information at the physiological level which could be of immediate value in the analysis of the pathogenesis of the infection, it did give morphological evidence for the opinion that some unidentified structural component of the virulent tubercle bacillus plays a dominant, essential role in its ability to manifest virulence. Indeed, more than that, the fact that this hypothetical component affects the mode of division and orientation of the bacilli during growth gave some confidence that the substance is at, or very close to, the surface of each bacterial cell.

Now let us consider the effects of the surface active agents which Dr. Dubos found useful for obtaining dispersed growth of tubercle bacilli in artificial media. They have effects of some interest on the colonial morphology of cultures. As illustrated in the accompanying schema, the wetting agent Tween 80 can, in sufficient concentration, render colonies of all strains of tubercle bacilli indistinguishable. They appear smooth, glistening, and hemispherical on agar, and in the depth of liquid media they show no evidence of cord formation—the bacilli are, for the most part, isolated one from another in dispersed state. When grown in the presence of a somewhat lower concentration of Tween 80, the virulent organisms show evidences of cord formation while the somewhat attenuated BCG strain and the avirulent strain show no evidence of this pattern of orientation.[9]

Virulent tubercle bacilli grown in the presence of concentrations of Tween 80 which entirely inhibit cord formation are no less infective for experimental animals. It was presumed, therefore, that the Tween which is rapidly hydrolyzed by animal tissues and fluids, as shown by Dr. Davis, merely masks some component of the surface of the virulent bacterial cells rather than preventing its synthesis or removing it from the surface of the bacterial cells. The lipophilic character of the Tween 80 molecule suggested further that the hypothetical substance directly responsible for cord formation might be, shall I say, a lipoidal substance. The implications of this hypothesis will be made more evident by Dr. Bloch.

Of equally great import for the third step of analysis is the discovery by Dr. Dubos of a striking cytochemical reaction which clearly distinguishes the cord-forming, virulent strains of tubercle bacilli from the non-cord-forming, avirulent variants.[11, 12] This reaction involves the adsorption by the cord-forming strains of the dye neutral red at alkaline pH. In aqueous solution at alkaline reaction neutral red is yellow in color; it is red at acid reactions. The cord-forming strains of tubercle bacilli living or killed with phenol are stained red by the dye while the dye in the surrounding fluid is yellow; the non-cord-forming strains are stained yellow under these conditions. It is known that this reaction is given by several acidic lipoidal substances—long-chain fatty acids, in particular. Although this reaction, therefore, is not chemically specific in the sense of an immunological reaction, it did emphasize the more clearly that the chemical structure of the surface of all virulent strains of mammalian tubercle bacilli differs in a special way from that of the non-cord-forming avirulent strains of the same subspecies of organisms.

It seems possible that further application of the scheme of analysis which I outlined earlier will yield fruits of significance for our understanding of pathogenesis and immunity in tuberculosis.

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A Component of Tubercle Bacilli Concerned with Their Virulence (ABSTRACT)

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The treatment of virulent tubercle bacilli with paraffin oil or lighter hydrocarbons results in the disruption of the bacillary "cords," a growth pattern characteristic for virulent strains of tubercle bacilli. In the same time a lipid material is obtained from young virulent bacilli extracted with these hydrocarbons. The yield is small and no such material can be extracted from avirulent variants of tubercle bacilli. Extracting the bacilli with paraffin oil, petroleum ether or similar compounds does not kill the organisms; after extraction, they are still able to grow on culture media. However, their biological behavior is changed. They do no longer inhibit the migration of leukocytes in vitro, and their state of pathogenicity for experimental animals is reduced. The lipid material obtained by extracting the cells exerts by itself, an inhibitory effect on leukocyte migration and is toxic for mice upon repeated injections of small doses. The lipid material is located at the surface of the bacillary cell, and extraction with petro-

leum ether alters the permeability of the cellular surface. This can be demonstrated by testing the methylene blue reducing power of both extracted and not extracted bacilli in the Thunberg tube. It was found that under standardized conditions, all virulent strains of mycobacteria tested so far did not decolorize methylene blue, whereas avirulent strains and saprophytic mycobacteria reduced the dye. This is due to a much greater permeability of the surface of avirulent cells. After treatment with petroleum ether, virulent strains also promptly decolorize methylene blue. With respect to this test, BCG and other attenuated strains behave like virulent organisms as long as they are young, but become methylene blue decolorizing by ageing. The time required for a culture incubated under standard conditions to become methylene blue reducing is proportional to the virulence of the strain. This is in good agreement with the fact that the lipid material mentioned earlier could only be obtained from young virulent cultures and, in smaller amounts from young cultures of mycobacteria of low virulence. The possible role of this bacterial constituent is seen in its interference with phagocytes and its toxic action which manifests itself after a necessary period of sensitization in extensive hemorrhagic lesions.

*Application of Virulence Studies to the Problems of BCG Immunization**

RENE J. DUBOS, CYNTHIA H. PIERCE and EMANUEL W. SUTER

The immunizing effect of BCG vaccination depends upon a certain degree of multiplication of the attenuated bacilli in the vaccinated host. The extent of this *in vivo* multiplication is conditioned by a number of independent factors. The following were discussed:

a) *The receptivity of the host tissues.* Certain physiological disturbances, such as caused by malnutrition or toxic influences, may allow BCG to cause extensive lesions in experimental animals without bringing about an increase in virulence of the culture.

b) *The number of living bacilli injected.* Different batches of vaccine prepared by the standard technique and obtained from recognized BCG laboratories were found to exhibit enormous differences in their content in living bacterial cells. In all of these vaccine preparations the number of viable cells was less than 1 per cent of the total number of cells. In the absence of quantitative information concerning the viability of the bacterial suspension, it is therefore meaningless and misleading to express doses of BCG in terms of mg. or cc. A technique was described for the preparation of BCG cultures in which the numbers of living cells remained high and constant for at least six weeks.

c) *The intrinsic virulence of the BCG culture.* Four strains of BCG were found to differ greatly in several of their biological characteristics. Moreover, each of these strains proved to be heterogeneous and yielded several colonial types when cultivated on oleic albumin agar. Isolation, subculture and description of different colonial types was reported. Work is in progress to define their comparative ability to multiply *in vivo* and to induce protective immunity.

Standardization of BCG vaccination would seem to require a more quantitative control of the number of living bacteria injected and greater uniformity of the bacterial population.

* From the Laboratories of The Rockefeller Institute for Medical Research, New York City.

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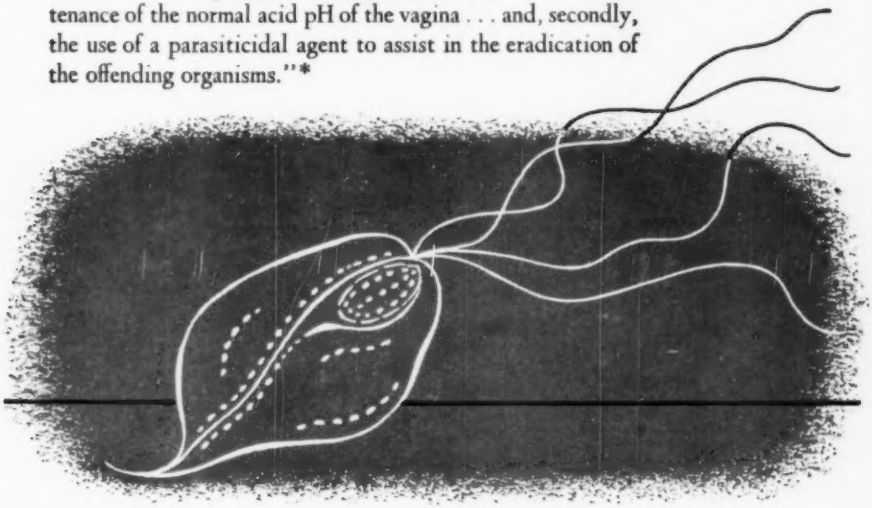

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*Hardy, J. W.: Office Gynecology, J. Missouri St. M. A. 45:811 (Nov.) 1948.

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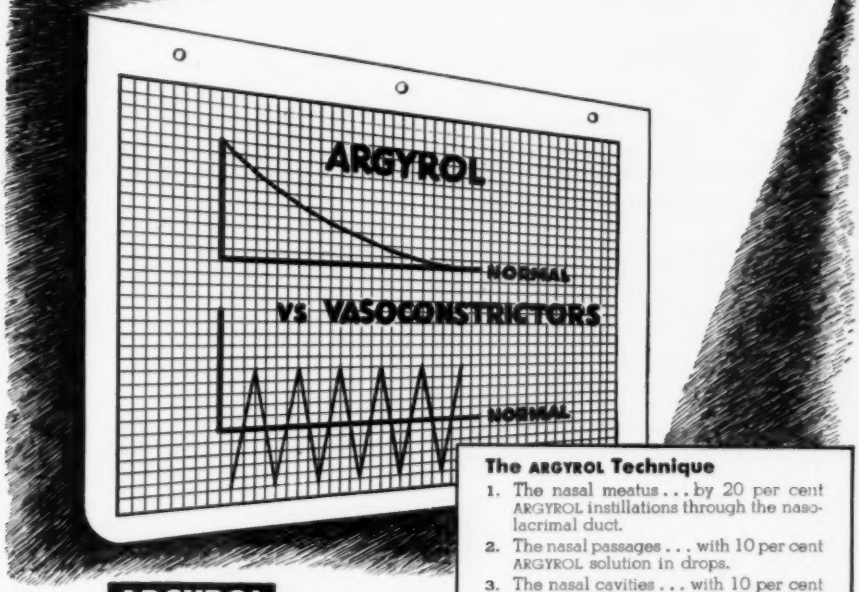

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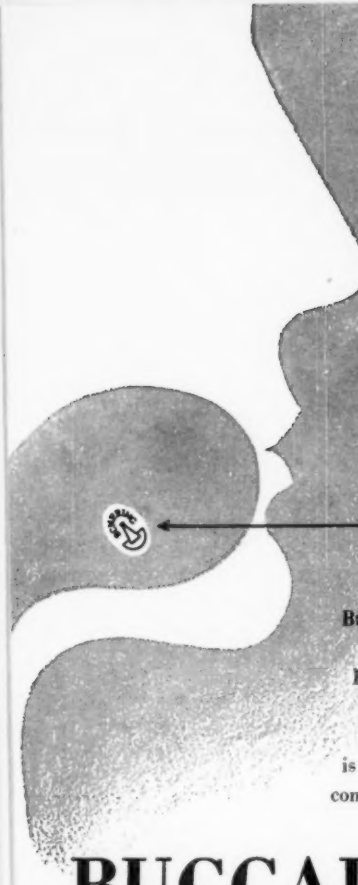

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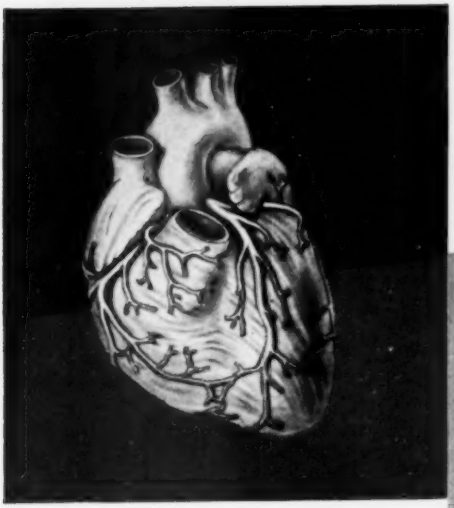

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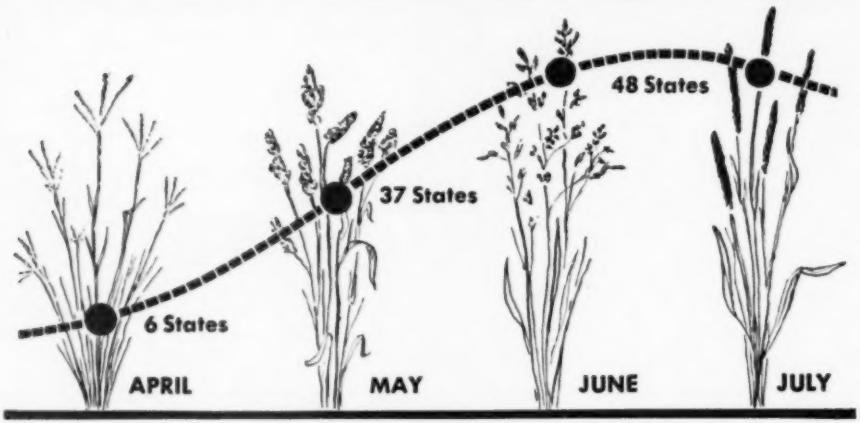

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